

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 14-778V

Filed: December 15, 2023

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JAMIE ROTHSTEIN,

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Petitioner,

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v.

Tetanus-diphtheria-acellular pertussis
("Tdap") Vaccine; Multiple Sclerosis
("MS"); Significant Aggravation

SECRETARY OF HEALTH
AND HUMAN SERVICES,

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Respondent.

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Curtis Webb, Esq., Curtis R. Webb, Attorney at Law, Monmouth, OR, for petitioner.

Katherine Edwards, Esq., U.S. Dept. of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT¹

Roth, Special Master:

On August 26, 2014, Jamie Rothstein ("Ms. Rothstein" or "petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*² ("Vaccine Act" or "Program"). Petitioner initially alleged that she received a tetanus-diphtheria-acellular pertussis vaccination on July 12, 2013, which caused her to develop transverse myelitis ("TM"). *See* Petition ("Pet."), ECF No. 1. On July 5, 2016, petitioner filed an Amended Petition alleging that the Tdap vaccination she received on July 12, 2013 caused "a significant aggravation of a preexisting, but asymptomatic, demyelinating neurologic disorder" which resulted in her development of MS. *See* Amended Petition ("Am. Pet.") at 1, ECF No. 36.

¹ Because this Ruling contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at <https://www.govinfo.gov/app/collection/uscourts/national/cofc>, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). This means the Ruling will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

² National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (1986). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2018).

Upon review of all the evidence, I find that petitioner has preponderantly demonstrated that the Tdap vaccine can trigger a relapse of MS in a susceptible person and did so in this case.

I. Procedural History

The petition was filed on August 26, 2014 and assigned to then Special Master Hamilton-Fieldman. *See* Pet., ECF No. 1, 4. Petitioner filed medical records on September 2, 2014 and January 29, 2015. Petitioner's Exhibit ("Pet. Ex.") 1-7, ECF No. 6, ECF No. 12-13, Pet. Ex. 8-11, ECF No. 14.

Respondent filed his Rule 4(c) Report on March 10, 2015, stating that the case was not appropriate for compensation. ECF No. 16.

Petitioner was ordered to file an expert report and additional medical records. ECF Nos. 17, 21-22; Pet. Ex. 12, ECF No. 23. Thereafter, petitioner filed several status reports regarding her search for new counsel. ECF Nos. 24, 26, 28, 30. The matter was reassigned to me on January 14, 2016. ECF Nos. 31-32. Petitioner filed a Motion to Substitute Counsel on March 21, 2016, which was granted. ECF No. 34.

An Amended Petition was filed on July 5, 2016. *See* Am. Pet., ECF No. 36. Petitioner filed an expert report and supporting literature on August 10 and 11, 2016. Pet. Ex. 13-45, ECF Nos. 38-43. Respondent filed an expert report and supporting literature on March 23, 2017. ECF Nos. 45-46; Respondent's Exhibits ("Resp. Ex.") A-I, ECF Nos. 47-49.

Additional medical records, two expert reports, and a motion for additional time to file records were all filed on July 26, 2017. Pet. Ex. 46-49, ECF Nos. 51-53. Petitioner filed additional medical literature and medical records on August 2 and 17, 2017. Pet. Ex. 50-79, ECF Nos. 54-58. Respondent filed a supplemental expert report on December 7, 2017. Resp. Ex. J-K, ECF No. 62. Petitioner filed additional expert reports on May 22, 2018 and medical records on February 5, 2019. Pet. Ex. 80-81, ECF No. 65-66; Pet. Ex. 88-92, ECF Nos. 76-77. Respondent filed a supplemental expert report and supporting medical literature on April 11, 2019. Resp. Ex. L-N, ECF No. 79.

Interim fees and costs were awarded on July 31, 2019. ECF Nos. 81-83.

A hearing was initially scheduled for March 26 and 27, 2020, but was later rescheduled for August 24 and 25, 2020. ECF Nos. 71, 96. Petitioner filed her pre-hearing submissions and updated medical records in February 2020. Pet. Ex. 93-97, ECF Nos. 89-93. Respondent filed his pre-hearing submissions on February 26, 2020. ECF No. 94. Petitioner filed her reply on March 12, 2020. ECF No. 97. Petitioner filed additional medical literature on July 27, 2020. Pet. Ex. 98-107, ECF No. 99. The parties filed a joint pre-hearing submission on August 5, 2020. Joint Stipulation, ECF No. 100. Petitioner filed a second pre-hearing submission the same day. ECF Nos. 101-02. On August 10 and 12, 2020, respondent filed additional pre-hearing submissions and medical literature. Resp. Ex. O-R, ECF Nos. 104-07. Respondent filed additional medical literature on August 20, 2020. Resp. Ex. S-T, ECF Nos. 108.

An entitlement hearing was held on August 24 and August 25, 2020. Petitioner and the experts Dr. Kinsbourne, Dr. Byers, and Dr. Sriram testified. After the hearing, petitioner filed further medical records and medical literature. Pet. Ex. 108-112, ECF No. 115. Post-hearing briefs were filed on May 25 and 26, 2021 after two motions for extensions of time were granted. ECF Nos. 117-20.

This matter is now ripe for adjudication.

II. Issues to be Determined

The parties stipulated to the following prior to the hearing:³

The parties agreed that a *Loving v. Sec'y of Health and Human Services*, 86 Fed. Cl. 135, 144 (2009) analysis should be used to determine whether the July 12, 2013 Tdap vaccine caused petitioner to suffer a significant aggravation of a preexisting condition. Joint Stipulation at 6.

For Prong 1 of *Loving*, the parties agreed that petitioner had no clinical symptoms of MS prior to receipt of the Tdap vaccine. Although the parties agreed that petitioner experienced an inflammatory process of the central nervous system, they disagreed on the medical and legal significance of petitioner's pre-vaccination central nervous system inflammation. Joint Stipulation at 6-7.

For *Loving* Prong 2, the parties agreed that petitioner developed clinical symptoms of MS the day after the Tdap vaccination which met the criteria for relapsing remitting MS⁴ based on clinical symptoms and MRI findings. Joint Stipulation at 7. They disagreed on the severity of petitioner's MS.

For *Loving* Prong 3, the parties disagreed that a comparison of petitioner's pre-vaccination and current condition shows a significant aggravation of her pre-vaccination condition. Joint Stipulation at 7.

For *Loving* Prong 4, the parties disagreed that petitioner had presented a reputable and reliable medical theory to support her allegation that the Tdap vaccine can cause a significant aggravation of her pre-vaccination condition. Joint Stipulation at 7.

For *Loving* Prong 5, the parties disagreed that a logical sequence of cause and effect showed petitioner's July 12, 2013 Tdap vaccination was the reason for any significant aggravation of her pre-vaccination condition. Joint Stipulation at 7.

³ Only the stipulations related to the main issues in this case are included herein. The Joint Stipulation can be found at ECF No. 100.

⁴ Multiple sclerosis is a disease in which there is demyelination throughout the central nervous system; symptoms usually include weakness, incoordination, paresthesias, speech disturbances, and visual complaints. Relapsing-remitting is one of four types of MS. *Dorland's Illustrated Medical Dictionary* 1653 (33rd ed. 2019) [hereinafter "Dorland's"].

For *Loving* Prong 6, the parties disagreed on whether any significant aggravation of petitioner's preexisting condition occurred within a timeframe that is medically acceptable to infer causation in fact. Joint Stipulation at 8.

At hearing, petitioner's counsel clarified, and her experts confirmed, that the opinions rendered in this case were that the body's inflammatory response to receipt of the Tdap vaccine was sufficient to trigger an asymptomatic, but already existing MS into active disease in a predisposed individual. Further, counsel explained that this case does not involve Tdap's ingredients as triggering petitioner's latent MS into active MS. Tr. 55-56, 74-75, 235-37, 247-48.

III. The Factual Record

a. Medical History

The following summary of the medical records contains only those facts most relevant to the disposition of this case, most of which were stipulated to by the parties, although an in-depth review of all the medical records was undertaken.

As a nurse, petitioner routinely received vaccines, including Tdap vaccinations in 1996, 2003, 2004, 2012 from various employers⁵ and an MMR vaccine on February 22, 2013. Tr. 250-51; Pet. Ex. 108 at 1, 4, 6; Pet. Ex. 109 at 2-4.

The parties stipulated to the relevant portions of petitioner's medical history following the Tdap vaccination. *See* Joint Stipulation at 1-6.⁶ The Joint Stipulation included the following: Petitioner received a Tdap vaccination on July 12, 2013. Pet. Ex. 3 at 1. The next day on July 13, 2013 petitioner began to feel pain and numbness on the bottom of her feet. Pet. Ex. 5 at 3, 5, 39. Between July 13 and August 18, 2013, the numbness in her legs progressively worsened and climbed up her legs to the level of her hips; she presented to the emergency room on August 18, 2013 with ascending weakness in both legs. *Id.* MRIs of her thoracic and lumbar spine were performed on August 24, 2013. MRIs of her cervical spine and brain were performed on August 28, 2013. MRI of the thoracic spine showed multifocal areas of abnormal signal in the thoracic cord and abnormal enhancement with central lesions at T6-T7. The leading consideration included demyelination.⁷ Pet. Ex. 2 at 25-26; Pet. Ex. 4 at 11-12, 14. MRI of the brain showed two areas of hyperintense signal which did not enhance and were nonspecific "but may represent sequelae of demyelinating disease." Pet. Ex. 1 at 13-14; Pet. Ex. 2 at 21-22; Pet. Ex. 4 at 16. Petitioner was initially diagnosed with post-vaccine transverse myelitis and treated with IVIG and prednisone. Pet. Ex. 1 at 5, 9, 12, 17-19. Repeat MRIs on December 17, 2013 showed no changes to the brain, stable lesions without new enhancement of the thoracic spine, mild patchy ventral T2 hyperintensity at C3 of the cervical spine, right dorsolateral T2 hyperintensity at C5, and a suggestion of left paracentral T2 lesion at T2. Pet. Ex. 6 at 9, 10, 13. Petitioner was hospitalized

⁵ The records petitioner located did not contain exact dates for all these vaccinations. Tr. 251.

⁶ Specific references to the medical records were not included in the Joint Stipulation but were added herein.

⁷ Demyelination refers to the destruction, removal, or loss of the myelin sheath of a nerve. Myelin sheath is the cylindrical covering on the axons of some neurons, consisting of concentric layers of myelin, formed by oligodendrocytes in the central nervous system. *Dorland's* 480, 1673.

with a relapse on March 18, 2017 with MRIs showing a new enhancing lesion at C3 with an old C6 lesion, and MS was believed to be the explanation for her symptoms; she was treated with IVIG and steroids. *See generally* Pet. Ex. 77; Pet. Ex. 78; Pet. Ex. 94; Pet. Ex. 96; Joint Stipulation at 1-6.

Other relevant medical history not contained in the Joint Stipulation includes the following.

No medical records were filed for the timeframe between December 23, 2013 and July 2014 when petitioner presented with continued complaints of pain in the bottom of her feet—more on the left—low back pain, and numbness and tingling traveling from her feet to her legs and back affecting her footing. She also reported headaches, blurred vision, left upper extremity pain and loss of sensation in the perineal area. Physical therapy (“PT”) was recommended. Pet. Ex. 6 at 5.

Petitioner’ next presentation was for PT on December 3, 2014. She reported feeling as though she was wearing compression stockings. It was noted that she had been diagnosed with “post-vaccinosis”. Pet. Ex. 10 at 2.

At her PT visit on December 8, 2014, she reported bilateral forearm and hand numbness and tingling, bilateral shoulder pain of 8/10, weakness, and unsteadiness in her lower extremities, near falls, difficulty with steps, and numbness and tingling and sharp pain in both feet. Onset was July 2013 following a reaction to a Tdap vaccine. Pet. Ex. 11 at 3. Petitioner attended PT for post-vaccine polyneuritis of the upper and lower extremities. *Id.* at 6.

Three years later, petitioner presented for repeat MRIs on January 30, 2017⁸ which indicated GBS. Pet. Ex. 76.

Petitioner was hospitalized on March 18, 2017 for ascending numbness and reports of urinary incontinence. MRI of the cervical spine showed a new enhancing lesion at C3. MRI of the brain showed a FLAIR intense periventricular lesion that could be consistent with MS. Pet. Ex. 78 at 3, 5; *see also* Pet. Ex. 77; Pet. Ex. 94; Pet. Ex. 96. MS was discussed as the most likely explanation for her symptoms. Petitioner asked if it was possibly triggered by her Tdap vaccination in 2013. Pet. Ex. 78 at 3. “It was explained to her that this seems less likely and that any seeming temporal association was likely coincidental.” *Id.* IV steroids were administered, and levothyroxine was prescribed. She was to follow up with Dr. Leist after discharge on March 21, 2017. *Id.* at 2-3.

Petitioner presented to Dr. Leist⁹ on April 4, 2017 for “presumptive post vaccination myelitis” from Tdap vaccine. Pet. Ex. 95 at 8; *see also* Pet. Ex. 79. She reported worsening of her lower extremity numbness ascending to her neck on March 13, 2017. She had new cervical and thoracic MRIs, which showed “[s]pot[s] concerning for demyelination.” She was diagnosed with MS and received five days of IV Solumedrol with improvement in dysesthesias. Pet. Ex. 95 at 8. She reported ongoing intermittent pins and needles and numbness, mostly on the bottom of her

⁸ No records were filed for the timeframe between December 8, 2014 and the January 30, 2017 MRIs. It is unclear who ordered the MRIs.

⁹ Dr. Leist routinely serves as an expert on behalf of respondent in the Program.

feet, fatigue, and visual and sleep disturbance. Pet. Ex. 95 at 13-14. Dr. Leist's impression was two distinct spinal cord episodes as of April 2017 with one lesion in the brain, suggestive of MS. Tecfidera—an MS disease modifying medication—was to be started. *Id.* at 11-12.

Petitioner continued to follow up with Dr. Leist. In 2018, her MRIs were unchanged. She was doing well on Tecfidera, although she had several falls and near falls due to ankle weakness. Pet. Ex. 95 at 44, 78-80, 103, 117, 125.

b. Affidavit and Testimony of Petitioner Jamie Rothstein

Petitioner's affidavit and testimony were consistent with the medical records. Petitioner received the Tdap vaccine on July 12, 2013, when hired as the Clinical Research Nurse Project Manager at Thomas Jefferson University Hospital ("Jefferson"). Pet. Ex. 93 at 1-2. The next day she experienced pain and numbness at the bottom of her feet. *Id.* at 2. She participated in a dog show that Saturday and felt like her feet were moving in cement. *Id.* She was unable to start her new position at Jefferson until July 23, 2013. *Id.* Between July 13 and August 18, 2013, the numbness got worse and rose up her legs to her waist. *Id.* On August 16, 2013, she fell running up the steps to catch the train for work and was injured. She finally decided to present to the ER due to concern for GBS. *Id.* at 3. An MRI was arranged, and she was prescribed Naproxen. *Id.*

Petitioner affirmed a diagnosis of TM following the MRIs. She received IV steroids. Pet. Ex. 93 at 3. The numbness and pain in her feet continued with pain shooting up her legs. She felt like she was wearing compression stockings, and walking was difficult. *Id.* She suffered several falls. *Id.* at 3-4.

Petitioner affirmed having to sell her family home due to her inability to navigate stairs safely. Pet. Ex. 93 at 4. She also could no longer show her dogs or walk distances. *Id.*

At the time of the Tdap vaccine, she had just been hired as a Clinical Research Nurse Manager for the Department of Surgery at Jefferson involved in managing multiple clinical research coordinators, data managers, and regulatory coordinators and over 120 clinical research trials, a majority of which were in oncology. Pet. Ex. 93 at 4. Working after her injury was difficult, her memory was affected, and her day-to-day tasks were challenging, but she maintained her workload. *Id.* at 4-5. She gained weight which affected how she felt about herself. *Id.* at 5.

Petitioner affirmed "being stable until March 2017" when she developed increased numbness in her inner thighs, groin, and up to her chest with urinary incontinence. Pet. Ex. 93 at 5. She was admitted to Jefferson, received IV steroid infusions, and was diagnosed with MS. *Id.* Since her relapse, her cognitive symptoms are worse, and her vision is poor. She experiences headaches and brain fog. *Id.* She was forced to resign from her position as a manager to take a lesser position. *Id.* at 6. She continues to have a host of symptoms, takes Tecfidera, and eats an anti-inflammatory diet. She can no longer maintain the active lifestyle she once enjoyed. *Id.*

At the entitlement hearing, petitioner testified to being a healthy and active wife, mother of two girls, registered nurse who walked twice daily, and a water safety instructor; she swam regularly and had no health issues prior to the subject Tdap vaccine. Tr. 8-10.

The Tdap vaccine was required when she accepted the position at Jefferson. Tr. 9. The vaccine was received at 8am on July 12, 2013. She awoke the following morning around 9am with her feet feeling “prickly, pins and needles,” “pain”, “odd”, “strange” and “numb” when she put them to the floor. Tr. 10-11, 27, 30-31. She and her dog participated in a dog show that weekend. She recalled falling in the grass during the warm-up. Tr. 11-13. When showing, she felt like she was moving in slow motion and her legs were in quicksand. Afterward, friends and family asked why she was moving so slowly but she gave it little thought over the busy weekend. Tr. 11-13.

Petitioner explained that she did not present to a doctor for 35 days because her husband had a stroke and she was busy scheduling therapies for him, getting her daughter ready for college in August, and had just started a new job. The symptoms started only on the bottom of her feet, then a few days later on the top of her feet; a couple of days later, the symptoms progressed to her ankles, calves, knees, then thighs. Tr. 13-14. In hindsight, she stated that she should have paid more attention. Tr. 14.

Petitioner recalled visiting the ER on August 18, 2013, being assessed, then being sent home because they could not offer an MRI at the time. She found Dr. Espaillat on her own who scheduled the MRIs for August 24 and 28, 2013. Tr. 14. He diagnosed her with transverse myelitis and prescribed IV steroids in her home for three days. Tr. 15. The IV steroids stopped the progression of the numbness, tingling, and pain which was, at that time, at her waist. Tr. 15. Petitioner stated she was symptomatic through 2016 but then got worse and felt like she was walking on broken glass. Tr. 16. Over time she noted issues with brain fog and memory, particularly at work. She started having difficulty walking around campus, falling several times, and getting lost. She awoke exhausted. Although she had trained her entire career for her position at the hospital, she now found the job taxing. It was painful to train and work with her dogs. Tr. 17-20.

Petitioner described her relapse in March 2017 as increasing numbness and pins and needles in her lower body that traveled up her trunk to her chest, shoulders, arms, and chin at which point she panicked and went to the ER because, as a nurse, she knew what it was like to be intubated. She was worried about her respiratory status. Tr. 20-21. She was admitted and administered IV Solumedrol for 7 days, which prevented the symptoms from progressing. Tr. 21.

When Dr. Espaillat passed away, she presented to Dr. Leist in April 2017 because he was in the same medical system and had access to her records. Tr. 33.

Currently, petitioner stated she has numbness from her chin down, painful joints with pain in her wrists, shoulders, knees, hips, ankles, fingers, blurry vision and is sad. She fears relapse. It hurts to walk and is sometimes painful to get out of bed. She fears falling, her neck hurts, she has ringing in her ears and electric shocks in her legs. She has warm flashes, cannot get cold, cannot get comfortable, and sees electric volts in her eyes at night. Tr. 25-26. She takes Tecfidera twice

daily since her relapse and eats an anti-inflammatory diet. Tr. 22. In July 2019, she took a pay cut and lesser job, as she was unable to perform her previous role. Tr. 23-25. She still drives but sometimes it is hard to see street signs and she gets lost, so she keeps her GPS on. Tr. 26-27. Petitioner filed a worker's compensation claim, but she did not recall anything happening with it. Tr. 31-32.

Petitioner confirmed receipt of work required vaccinations over the years including Tdap vaccines in 2012, 2004, 2003, 1996 and the subject vaccine on July 12, 2013. Tr. 250-51.

IV. Expert Opinions

At the time of the hearing, petitioner clarified that she was not alleging that the Tdap vaccine or any of its ingredients caused her MS. Her theory in this case was that she suffered an inflammatory response following receipt of the Tdap vaccine, which was sufficient to trigger her already existing but asymptomatic MS. Specifically, the inflammatory response caused the enhancement of an existing but asymptomatic lesion present on her thoracic spine, resulting in the symptoms she suffered the day following her receipt of the Tdap vaccine.

All experts agreed that the non-enhancing lesions seen on the August 28, 2013 MRI indicated that an asymptomatic demyelinating neurological disorder existed prior to her July 12, 2013 Tdap vaccination. Joint Stipulation at 3.

I have read all the submissions by the experts in this case, as well as all the literature upon which they rely, but will only address those opinions that relate to petitioner's theory presented at hearing.

a. Petitioner's Expert, Dr. Marcel Kinsbourne

Dr. Marcel Kinsbourne graduated from Oxford University in England with a B.M., B.Ch., the equivalent of an American M.D. Pet. Ex. 14 at 2. Dr. Kinsbourne became licensed in the United States in 1967. *Id.* Dr. Kinsbourne served as an associate professor and a senior research associate at Duke University Medical Center before holding a series of academic positions. *Id.* at 2-3. His clinical experience includes serving as a senior staff physician in Ontario from 1974-1980 and a clinical associate in neurology at Massachusetts General Hospital from 1981-1991. *See Fantini v. Sec'y of Health & Human Servs.*, No. 15-1332V, 2022 WL 1760730, at *5 (Fed. Cl. Spec. Mstr. May 2, 2022).

Dr. Kinsbourne's credentials as a neurologist were stipulated to. Tr. 35. He is not an immunologist and is not trained or certified as one. Tr. 62-63. Dr. Kinsbourne rarely treats patients anymore. Tr. 64. He reads MRIs but is not a radiologist and when he was in practice, he relied on the radiologists to read the MRIs. Tr. 64. He diagnosed patients with MS in the early-to mid-1990s. Tr. 64. In 1995, he took a position at the New School and his clinical practice stopped. Tr. 64-65. Though he could not recall, Dr. Kinsbourne was sure he has treated patients with RRMS but stated that it would have been in the 1990s. Tr. 65.

Dr. Kinsbourne is well known to the Court having been involved in Vaccine Program cases since the inception of the Program. *See, e.g., Badman v. Sec'y of Health & Human Servs.*, No. 89-89V, 1990 WL 293393, at *1 (Fed. Cl. Spec. Mstr. Mar. 22, 1990).

Dr. Kinsbourne issued three reports in this matter and testified at hearing. Pet. Ex. 13; Pet. Ex. 49; Pet. Ex. 81.

i. Dr. Kinsbourne's First Report

Dr. Kinsbourne's first report concentrated on petitioner's initial diagnosis of TM.¹⁰ Dr. Kinsbourne described TM as an acute focal inflammatory disorder of the spinal cord that destroys the myelin—or sheaths of the nerve fibers—interrupting communication between the affected area of the spinal cord and other parts of the body. Pet. Ex. 13 at 3. TM is associated with systemic inflammatory diseases such as Sjogren's, systemic lupus erythematosus, and neurosarcoidosis; non-inflammatory causes include spinal cord injury, compression, post radiation, neoplastic, and vascular issues. *Id.* TM has also been linked to viruses, bacteria, parasites, and vaccines, including tetanus toxoid. *Id.* at 4.¹¹

Dr. Kinsbourne submitted that TM is an autoimmune process that can be induced by vaccination. Pet. Ex. 13 at 4; Pet. Ex. 28.¹² He relied on *Agmon-Levin et al.*, a study of 37 cases of TM associated with 11 different vaccines or combinations of vaccines which concluded that the pathogenesis of TM is mostly autoimmune triggered by environmental factors including vaccinations. Pet. Ex. 13 at 4; Pet. Ex. 15 at 2.¹³ In Dr. Kinsbourne's opinion, vaccines and infections are similar; if an infectious agent can cause TM, so can the recombinant or live attenuated antigens used in a vaccine. Pet. Ex. 13 at 4; Pet. Ex. 15 at 5.

Dr. Kinsbourne discussed the innate or initial immune response to a vaccine or infection, submitting that the authors of *Netea et al.* found that, in addition to the adaptive immune system, the innate immune system harbors memory allowing for a quicker immune response. "Innate immune responses induced by exposure to one pathogen or vaccine can affect the immune response to another." Pet. Ex. 103 at 678-79;¹⁴ Pet. Ex. 13 at 8-9. *Merson* showed that the outpouring of proinflammatory cytokines, e.g. tumor necrosis factor ("TNF"), IL-1, IL-6 and IL-17, and chemokines act in concert to amplify the inflammatory response and can exert cytotoxic effects on the brain leading to demyelination and axonal pathology. Pet. Ex. 31.¹⁵ These

¹⁰ Dr. Kinsbourne's opinions regarding TM are included in the following discussion, as many aspects of TM and MS overlap.

¹¹ Dr. Kinsbourne cited to Menkes et al. 2006 in support of this assertion; however, it appears this article was not filed.

¹² Douglas A. Kerr & Harold Ayetey, *Immunopathogenesis of Acute Transverse Myelitis*, 15 CURRENT OPINION IN NEUROLOGY 339 (2002), filed as "Pet. Ex. 28."

¹³ N. Agmon-Levin et al., *Transverse Myelitis and Vaccines: A Multi-Analysis*, 18 LUPUS 1198 (2009), filed as "Pet. Ex. 15."

¹⁴ Mihai G. Netea et al., *Innate Immune Memory: A Paradigm Shift in Understanding Host Defense*, 16 NATURE IMMUNOLOGY 675 (2015), filed as "Pet. Ex. 32" and "Pet. Ex. 103."

¹⁵ Tobias D. Merson, *Role of Cytokines as Mediators and Regulators of Microglial Activity in Inflammatory Demyelination of the CNS*, 12 NEUROMOLECULAR MED. 99 (2010), filed as "Pet. Ex. 31."

proinflammatory cytokines are generated by the innate immune system and can trigger MS relapse, even without a previous exposure to the Tdap antigen. Further, *Hofer & Campbell* documented the destructive nature of the proinflammatory cytokine IL-6 generated by the innate immune system in causing immunoinflammatory disease, demyelination, and axonal damage in the spinal cord. Pet. Ex. 13 at 9; Pet. Ex. 26.¹⁶

Dr. Kinsbourne explained that the short onset of petitioner's symptoms was consistent with an anamnestic response. Pet. Ex. 13 at 8. He explained that an anamnestic response "denotes a secondary immune response that occurs with a second or subsequent exposure to an antigen." *Id.* When there is a second exposure to an antigen, the innate immune system responds quickly by releasing pro-inflammatory cytokines. *Id.*

Dr. Kinsbourne clarified that he was not saying the vaccine itself can cause TM/MS lesions but rather it is the body's inflammatory reaction to the vaccine that can trigger existing latent TM/MS lesions to become active. Pet. Ex. 13 at 5-6.

ii. Dr. Kinsbourne's Second and Third Reports

Dr. Kinsbourne issued two additional reports following petitioner's diagnosis of MS, submitting that both infectious processes and vaccines are capable of triggering an MS relapse. Pet. Ex. 49 at 1; Pet. Ex. 81; Pet. Ex. 99.¹⁷

Dr. Kinsbourne noted that vaccines contain infectious antigens, either attenuated or recombinant, and though rarely, may induce autoimmunity. Pet. Ex. 49 at 1; Pet. Ex. 53 at 1127.¹⁸ Dr. Kinsbourne explained that the tetanus toxoid contained in Tdap is a potent immunogen that elicits high antibody titers and produces long-lasting immunity by stimulating a rapid outpouring of proinflammatory cytokines, notably TNF alpha, IL-1 beta, IL-1 alpha, and IL-6. Pet. Ex. 13 at 5; Pet. Ex. 101.¹⁹ Tetanus toxoid is "well known to be capable of inducing immune-mediated neurological disorders" including TM. Pet. Ex. 13 at 5; Pet. Ex. 37;²⁰ Pet. Ex. 38;²¹ Pet. Ex. 43;²²

¹⁶ MJ Hofer & IL Campbell, *Immunoinflammatory Diseases of the Central Nervous System – the Tale of Two Cytokines*, 173 BRITISH J. OF PHARMACOLOGY 716 (2016), filed as "Pet. Ex. 26."

¹⁷ D. Buljevac et al., *Prospective Study on the Relationship Between Infections and Multiple Sclerosis Exacerbations*, 125 BRAIN 952 (2002), filed as "Pet. Ex. 18" and "Pet. Ex. 99."

¹⁸ Y. Shoenfeld, *Infections, Vaccines and Autoimmunity*, 18 LUPUS 1127 (2009), filed at "Pet. Ex. 40" and "Pet. Ex. 53."

¹⁹ Victor Fernandez et al., *Cytokine Synthesis Analyzed at the Single-Cell Level Before and After Revaccination with Tetanus Toxoid*, 24 EUR. J. OF IMMUNOLOGY 1808 (1994), Filed as "Pet. Ex. 21" and "Pet. Ex. 101."

²⁰ Stephen J. Read et al., *Acute Transverse Myelitis After Tetanus Toxoid Vaccination*, 339 LANCET 1111 (1992), filed as "Pet. Ex. 37."

²¹ S. Lane Rutledge, M.D., & O. Carter Snead III, M.D., *Neurologic Complications of Immunization*, 109 J. OF PEDIATRICS 917 (1986), filed as "Pet. Ex. 38."

²² F. Tezzon et al., *Acute Radiculomyelitis After Antitetanus Vaccination*, 15 ITALIAN J. OF NEUROLOGICAL SCI. 191 (1994), filed as "Pet. Ex. 43."

Pet. Ex. 44;²³ Pet. Ex. 45;²⁴ Pet. Ex. 81 at 1. The Institute of Medicine (“IOM”) has concluded that causation of central nervous system (“CNS”) disease, including TM, by tetanus toxoid is biologically plausible. Pet. Ex. 81 at 1-2; Pet. Ex. 42.²⁵ *Kashiwagi et al.* showed that innate immune response to Tdap is similar to the innate immune response to H1N1 influenza; thus, it need not be a live vaccine to provoke autoimmune reactions. Pet. Ex. 81 at 2; Pet. Ex. 106.²⁶ *Kashiwagi et al.* concluded that “[a]ll effective vaccines induce acquired immunity with the development of antigen-specific antibodies and/or cell-mediated immunity, and the stimulation of innate immunity is now considered essential.” Pet. Ex. 106 at 678.

Dr. Kinsbourne added that *Kaplin et al.* found, regardless of cause, “IL-6 levels were selectively and dramatically elevated in the cerebrospinal fluid in TM patients and directly correlated with markers of tissue injury and sustained clinical disability.” Pet. Ex. 13 at 5; Pet. Ex. 27 at 2731.²⁷ Pathological specimens of TM patients included astrocytes which have been shown to produce IL-6 in response to direct stimulation by proinflammatory cytokines like TNF- α and IL-1 β , viral and bacterial pathogens, and neurotransmitters. *Kaplin et. al.* concluded that “[p]otential triggers include an immune response following vaccination or an antecedent infection that could involve mechanisms such as molecular mimicry or superantigen-mediated inflammation.” Pet. Ex. 13 at 5; Pet. Ex. 27 at 2733.

Dr. Kinsbourne relied on Dr. Sriram’s studies in support of petitioner’s theory that TM/MS lesions can be triggered by inflammation generated from an infection or vaccine. Pet. Ex. 49 at 2. Dr. Sriram’s studies use pro-inflammatory cytokine antagonists, cytokine receptor antagonists, and compounds that interfere with signal transduction pathways in autoimmune models of experimental allergic encephalitis (“EAE”) for the development of therapeutic strategies in hopes that they can be used in humans with demyelinating disease such as MS. *Id.* In one such study, the authors—including Dr. Sriram—found that “[c]lose similarities between MS and the animal model of the disease experimental allergic encephalomyelitis (EAE) suggested that MS might be an autoimmune disease which is triggered by an infectious agent.” Pet. Ex. 49 at 2; Pet. Ex. 50.²⁸ In a later study, *Deng & Sriram* concluded that the presentation of neuronal autoantigens to autoreactive T cells by microglia²⁹ and the attendant secretion of proinflammatory cytokines were thought to facilitate the inflammatory process in diseases such as MS. Pet. Ex. 49 at 2; Pet. Ex.

²³ Haluk Topaloglu et al., *Optic Neuritis and Myelitis After Booster Tetanus Toxoid Vaccination*, 339 LANCET 178 (1992), filed as “Pet. Ex. 44.”

²⁴ Eileen Whittle & NRC Roberton, *Transverse Myelitis After Diphtheria, Tetanus, and Polio Immunisation*, 1 BRITISH MEDICAL J. 1450 (1977), filed as “Pet. Ex. 45.”

²⁵ Kathleen R. Stratton et al., *Adverse Events Associated with Childhood Vaccines*, Institute of Medicine (1994), filed as “Pet. Ex. 42.”

²⁶ Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenzae Type B (Hib), and 7-valent Pneumococcal (PCV7) Vaccines*, 10 HUM. VACCINES & IMMUNOTHERAPEUTICS 677 (2014), filed as “Pet. Ex. 63” and “Pet. Ex. 106.”

²⁷ Adam I. Kaplin et al., *IL-6 Induces Regionally Selective Spinal Cord Injury in Patients with the Neuroinflammatory Disorder Transverse Myelitis*, 115 THE J. OF CLINICAL INVESTIGATION 2731 (2005), filed as “Pet. Ex. 27.”

²⁸ John J. Bright & Subramaniam Sriram, *Immunotherapy of Inflammatory Demyelinating Disease of the Central Nervous System*, 23 IMMUNOLOGIC RES. 245 (2001), filed as “Pet. Ex. 50.”

²⁹ Microglia are the small, nonneuronal, interstitial cells that form part of the supporting structure of the central nervous system. *Dorland’s* 1143.

100 at 239.³⁰ This suggested that the autoimmune etiology for MS was not limited to molecular mimicry. Pet. Ex. 49 at 2. That same year, *Sriram & Steiner* published another study resulting in the belief that available pathogenic and radiological data argues favorably in examining issues outside the “autoimmune hypothesis” as central elements of the disease process. Pet. Ex. 49 at 2; Pet. Ex. 54 at 6.³¹ In 2010, *Patawe & Sriram* concluded that “[v]iral and bacterial infections have been shown to be associated with disease exacerbations” in relapsing remitting multiple sclerosis. Pet. Ex. 49 at 2; Pet. Ex. 52.³²

Dr. Kinsbourne argued that despite Dr. Sriram’s own research confirming that viral and bacterial infections can trigger relapses of MS, Dr. Sriram rejects the Tdap vaccination as a trigger in this case. Pet. Ex. 49 at 2. Instead, Dr. Sriram relied on *DeStefano et al.*, which Dr. Kinsbourne described as a negative epidemiological study structured in such a way as to be unlikely to uncover rare events such as MS relapse triggered by vaccination. *Id.*; Resp. Ex. E.³³

Dr. Kinsbourne also addressed Dr. Sriram’s reliance on *Mailand & Frederiksen*, which studied metadata on the relationship between vaccinations and onset or relapse of MS. Pet. Ex. 49 at 2-3; Resp. Ex. F.³⁴ Dr. Sriram claimed the review identified 11 studies that failed to relate onset or relapse of MS to the tetanus vaccine; however, Dr. Kinsbourne argued that none of the 11 studies focused on tetanus vaccine, three focused on vaccines in general, one on influenza, one on Hepatitis B, and six addressed the etiology of MS in general or in the context of risk factors, environmental factors, or infections. *Id.* Tdap was not included in the survey and the admitted limitations of the research explained many reasons for their inability to detect rare events, such as vaccine injuries. *Id.*

Dr. Kinsbourne maintained that if infections can precipitate autoimmune disease, so can vaccinations. Pet. Ex. 49 at 3. He relied on *Balofsky et al.* which found that adverse events from vaccines include the rare severe reaction of hypersensitivity, induction of actual infection, or autoimmune phenomenon. *Id.*; Pet. Ex. 17.³⁵ Dr. Kinsbourne concluded that it is the immune response to infections that can cause relapse in MS and vaccines are constructed to elicit a comparable immune response. Pet. Ex. 81 at 1.

Dr. Kinsbourne interpreted Dr. Sriram’s statement that “it is highly unlikely that the immune response which triggered the relapsing remitting MS was capable of being activated and expanded in one day” to mean Dr. Sriram’s primary issue in this case was with the short onset

³⁰ Xinqing Deng, MD, MPH & Subramaniam Sriram, MD, *Role of Microglia in Multiple Sclerosis*, 5 CURRENT NEUROLOGY & NEUROSCIENCE REPORTS 239 (2005), filed as “Pet. Ex. 20” and “Pet. Ex. 100.”

³¹ Subramaniam Sriram, MD & Israel Steiner, MD, *Experimental Allergic Encephalomyelitis: A Misleading Model of Multiple Sclerosis*, 58 ANNALS OF NEUROLOGY 939 (2005), filed as “Pet. Ex. 54.”

³² Siddharama Pawate & Subramaniam Sriram, *The Role of Infections in the Pathogenesis and Course of Multiple Sclerosis*, 13 ANNALS OF INDIAN ACADEMY OF NEUROLOGY 80 (2010), filed as “Pet. Ex. 52.”

³³ Frank DeStefano, MD, MPH et al., *Vaccinations and Risk of Central Nervous System Demyelinating Diseases in Adults*, 60 ARCHIVES OF NEUROLOGY 504 (2003), filed as “Resp. Ex. E.”

³⁴ Mia Topsoe Mailand & Jette Lautrup Frederiksen, *Vaccines and Multiple Sclerosis: A Systematic Review*, 264 J. OF NEUROLOGY 1035 (2017), filed as “Resp. Ex. F.”

³⁵ Ari Balofsky et al., *The New H1N1 and HPV Vaccines and Old Fears*, 22 CURRENT OPINION IN RHEUMATOLOGY 1 (2010), filed as “Pet. Ex. 17.”

between the Tdap vaccination and onset of symptoms. Dr. Kinsbourne deferred to Dr. Byers to explain the rapid onset. Pet. Ex. 49 at 3.

Dr. Kinsbourne concluded that tetanus toxoid can provoke clinically apparent MS—albeit rarely—and did significantly aggravate petitioner's subclinical MS and can do so quickly, as explained by Dr. Byers. Pet. Ex. 13 at 10; Pet. Ex. 49 at 3; Pet. Ex. 81 at 2.

iii. Dr. Kinsbourne's Testimony

Dr. Kinsbourne made clear "...the vaccination did not trigger or cause MS. That had already happened, as we learned from the MRI...in August of 2013, so the condition—the demyelination tendency was there, but it had not yet been triggered up to the clinical level." Tr. 41, 74. The Tdap vaccine transformed an asymptomatic MS into "clinically handicapping" MS. Tr. 41. For this to happen, the person must be susceptible or vulnerable. Tr. 106.

Dr. Kinsbourne explained that any agents that cause inflammation in the brain or spinal cord can aggravate existing MS. Tr. 41. Various infections, even mild infections, have this capability. Tr. 41-42. It is a combination of events that is potentially inflammatory in a person who is susceptible. Tr. 41-42. Relapses can either be a manifestation of new symptoms, a worsening of existing symptoms, or both. Tr. 44. Changes are typically seen radiologically, and sometimes the progression of lesions can be seen even in the absence of symptoms. Tr. 44. Further, sufficient evidence exists supporting infections triggering or exacerbating MS in a susceptible person. Tr. 106. Succinctly, the inflammation following petitioner's Tdap vaccine exacerbated a previously asymptomatic MS, which became clinical and handicapping. Tr. 75-76.

Dr. Kinsbourne stated both the medical community and literature accept and support that infections and vaccines can cause inflammation that triggers MS relapses. Tr. 43-44, 48, 105. *Buljevac et al.* concluded "... at least in the [relapsing/remitting] phase—the level of inflammatory activity influences the extent of structural brain damage. Thus, any factor that increases inflammatory activity could contribute to neurological deterioration." Tr. 42-43. Vaccines are one of many factors that could contribute to inflammatory activity. Tr. 42-43, 47-48; Pet. Ex. 99 at 953.³⁶ Dr. Kinsbourne agreed *Buljevac et al.* studied exacerbation of MS with infection not vaccines and took an average 9.5 days for relapse following onset of infection, but he stated the study failed to provide the distribution that comprised the average. Tr. 96-98. Thus, *Buljevac et al.* does not refute petitioner's position that onset could happen in less than one day. Tr. 97.

Dr. Kinsbourne stated *Libbey et al.* showed that infections can trigger a relapse of MS. Tr. 105; Pet. Ex. 102.³⁷ He conceded that *Libbey et al.* did not study vaccines but concluded that "[d]isease potentiation could occur indirectly through nonspecific stimulation of immune responses." Tr. 106; Pet. Ex. 102. Dr. Kinsbourne argued that vaccines like infection stimulate the immune system, so the finding applies to both. Tr. 106-07; Pet. Ex. 102 at 9. He reiterated that infections or vaccines do not cause MS, but rather the body's inflammatory response to both in a

³⁶ Buljevac et al., *supra* note 17.

³⁷ Jane E. Libbey et al., *Role of Pathogens in Multiple Sclerosis*, 33 INT'L REV. OF IMMUNOLOGY 266 (2014), filed as "Pet. Ex. 29" and "Pet. Ex. 102."

susceptible person can trigger already present lesions to become active. Tr. 106. Dr. Kinsbourne conceded *Steelman* discussed infections, not vaccines, as a trigger or exacerbation of MS but its model showed that peripheral infection induces neuroinflammation in T cell mediated relapse of MS by both innate and adaptive immune responses. He however deferred to Dr. Byers on the immunology. Tr. 110-11; Pet. Ex. 104 at 9, Figure 2.³⁸

Dr. Kinsbourne added that in *Fernandez et al.*, tetanus toxoid was given to volunteers with cytokine levels compared before and after administration.³⁹ Tr. 102. The authors found that Tdap increased cytokine levels. Tr. 101; Pet. Ex. 101.⁴⁰ He agreed that testing was not done within 24 hours of vaccination. Tr. 103. He again deferred to Dr. Byers for questions of timing. Tr. 103-04.

Dr. Kinsbourne referenced *Kashiwagi et al.* to show that the Tdap vaccine causes an innate immune response that can occur in less than 2 hours after vaccination with substantial inflammatory cytokine response after six hours that continues for the rest of the day. Tr. 50-51; Pet. Ex. 106 at 680.⁴¹ Comparing Tdap, Hib, and pneumococcal conjugate vaccines with mild influenza infection, *Kashiwagi et al.* found no difference in IL-16 and TNF-alpha levels between vaccine recipients and influenza patients. Tr. 50-51. Dr. Kinsbourne argued that this showed that inflammatory activation after infection is similar to vaccination during the first day after administration, adding that vaccines are meant to mimic the immunity of a wild virus. Tr. 55. Here, the Tdap vaccine was the inflammatory stimulus that caused an exacerbation of petitioner's preexisting asymptomatic MS lesion on the thoracic spine to the point of being clinically apparent with active inflammation seen on the MRI. Tr. 56-57. Dr. Kinsbourne added that inflammation generated by vaccination is not usually intense enough to cause harm, but petitioner was uniquely susceptible, and the stimulus was sufficient to raise the level of inflammation in the thoracic lesion to cause clinical harm. No alternative cause existed. Tr. 56-57. *Kashiwagi et al.* showed this inflammatory process could have occurred within hours. Tr. 57; Pet. Ex. 106.

Dr. Kinsbourne offered *Serres et al.*, where brain lesions were caused in rats and once the inflamed lesions calmed down, an inflammatory stimulus called lipopolysaccharide ("LPS")⁴² was administered, which reactivated the lesions within hours and certainly within a day. Tr. 58-59; Pet. Ex. 107.⁴³ *Andersen et al.* also showed relapses of lesions within a two-week post-infection period demonstrating that "max frequency peaked during the first and second week after the onset of a common infection." Dr. Kinsbourne interpreted that to mean anywhere within that timeframe, which includes within one day. Tr. 94-96; Pet. Ex. 98 at 419.⁴⁴

³⁸ Andrew J. Steelman, *Infection as an Environmental Trigger of Multiple Sclerosis Disease Exacerbation*, 6 FRONTIERS IN IMMUNOLOGY 520 (2015), filed as "Pet. Ex. 41" and "Pet. Ex. 104."

³⁹ When questioned further, Dr. Kinsbourne conceded that the blood samples were collected immediately before vaccination and nine weeks after. Tr. 102.

⁴⁰ Fernandez et al., *supra* note 19.

⁴¹ Kashiwagi et al., *supra* note 26.

⁴² Lipopolysaccharide is used to amplify the immune response in animal models but is not contained in vaccines. Tr. 121, 158, 160.

⁴³ Sebastien Serres et al., *Systemic Inflammatory Response Reactivates Immune-Mediated Lesions in Rat Brain*, 29 THE J. OF NEUROSCIENCE 4820 (2009), filed as "Pet. Ex. 70" and "Pet. Ex. 107."

⁴⁴ Oluf Andersen et al., *Viral Infections Trigger Multiple Sclerosis Relapses: A Prospective Seroepidemiological Study*, 240 J. OF NEUROLOGY 417 (1993), filed as "Pet. Ex. 16" and "Pet. Ex. 98."

When asked about *Hapfelmeier et al.*, a large case-controlled study which failed to find vaccinations as a risk factor for MS, Dr. Kinsbourne stated that the study discussed vaccines as a cause of MS, while he was discussing vaccines exacerbating an already existing MS. Tr. 114-15; Resp. Ex. S at 8-9.⁴⁵

Dr. Kinsbourne stated like any drug, Tdap and other vaccines on occasion can cause harm to a susceptible person. Tr. 45, 49. Petitioner had a preexisting lesion present on the thoracic spine that was not yet inflamed enough to cause clinical problems. It simply took an inflammatory challenge caused by the vaccine to raise inflammation to a clinical level. Tr. 48-49. Had an MRI been done prior to her Tdap vaccine, she would have had radiological MS that did not yet meet clinical diagnosis. Tr. 68. The August 2013 brain MRI also showed non-enhancing demyelinating lesions in the right posterior cerebral hemisphere unrelated to her clinical manifestations. Tr. 39-40, 68. The MRI of the spine showed hyperintensities posteriorly from the cervical spine to the thoracic spine, first thought to be TM but then identified as MS. These spinal cord lesions were latent prior to the Tdap vaccine. Tr. 36, 68-69. Dr. Kinsbourne noted that the spinal cord lesions were across both sides of the cord at various levels, each lesion occupying only one or two segments; this presentation is distinct from TM where the lesion is longitudinally extensive over multiple segments. Tr. 37-38. Dr. Kinsbourne stated that new enhancing lesions are characterized by inflammation around blood vessels that cause acute relapse through the migration of lymphocytes from the blood into the brain, similar to the response when autoimmune T cells enter the brain. Tr. 67. Following the Tdap vaccine, the lesion at T5-6 was active on MRI or “enhanced with gadolinium” while the other lesions remained unenhanced. Tr. 38. The location of the enhanced lesion was responsible for her development of sensory system issues and painful paresthesia arising from the soles of her feet and “landing at the level of her waist.” Tr. 37. Whether she had inflammation at some point prior to her vaccination is unknown. But the MRI in August 2013 showed inflammation on the spinal cord that corresponded with her clinical disability. Tr. 70. There is no way to know whether the asymptomatic lesions that existed prior to the Tdap vaccine would have become symptomatic had petitioner not received the vaccine. Tr. 37.

Dr. Kinsbourne could not say when the lesion first enhanced, but enhanced lesions persist radiographically for 4-6 weeks—not indefinitely. Tr. 69, 71. He did not know if there is lag between development of symptoms once enhancing lesions develop. Tr. 70. He agreed the duration of enhancing lesions can vary, that lesions can be enhanced without symptoms, and that the date of enhancement and onset of symptoms can differ. Tr. 73-74. However, here, the enhanced/active lesion seen on the thoracic spine MRI was consistent with disturbance of the spinal cord function and was the cause of her symptoms documented in the medical record as ascending numbness in both legs with pins and needles in both feet that progressed to her buttocks and abdomen. Tr. 38, 69, 76-77; Pet. Ex. 5 at 5.

Acknowledging petitioner’s onset of symptoms was within one day, Dr. Kinsbourne stated there are no prior MRIs to show if she had enhancing lesions prior to the vaccination. Tr. 40, 70-71. However, *O’Riordan et al.*, *Maia et al.*, and *Hakiki et al.* support his opinion that not all non-

⁴⁵ Alexander Hapfelmeier, PhD et al., *A Large Case-Control Study on Vaccination as Risk Factor for Multiple Sclerosis*, 93 NEUROLOGY e908 (2019), filed as “Resp. Ex. S.”

enhancing lesions had to have been enhanced at some point in time. Tr. 71-72; Pet. Ex. 25;⁴⁶ Pet. Ex. 30;⁴⁷ Pet. Ex. 34.⁴⁸

Dr. Kinsbourne agreed that petitioner's relapse in March 2017 with a new enhancing lesion at C3 was not precipitated by vaccine, infection, or fever. Tr. 77-79; Pet. Ex. 96 at 6, 33.

Dr. Kinsbourne concluded that petitioner's Tdap vaccine was a substantial factor in triggering her preexisting MS to a symptomatic level. Tr. 59. She could have remained asymptomatic for the rest of her life otherwise. Having been previously asymptomatic, petitioner's initial symptoms were not technically a relapse. But once the clinical manifestations of MS began, it took on a relapsing/remitting course, ultimately leaving her with increasing disability. Tr. 59, 67-68.

b. Petitioner's Expert, Dr. Vera Byers

Dr. Byers is an internist, immunologist, and toxicologist. Pet. Ex. 111 at 1. She obtained her M.A. in Microbiology in 1967 and her Ph.D. in Immunology in 1969, both at the University of California at Los Angeles. *Id.* at 4. She later obtained her M.D. in 1981 from the University of California at San Francisco, where she also served as a fellow, an adjunct professor, and a consultant. *Id.* at 5, 7. Dr. Byers completed her residency in internal medicine and her postdoctoral fellowship in cancer immunotherapy and clinical immunology. *Id.*

Her expertise as a clinical immunologist was stipulated to and she was qualified as an expert in immunology. Tr. 117-18. She has not had a clinical practice since 2002 but still sees the patients she had before she closed her practice. Tr. 128-29. Dr. Byers confirmed that she has treated RRMS patients. Tr. 129. At the time of hearing, her primary source of income was in vaccine and toxicology litigation, as well as litigation regarding the environmental causes of cancer. Tr. 130. Dr. Byers has not published on MS and could not recall if she published on cytokine response to vaccines. Tr. 130.

Dr. Byers issued two expert reports and testified at hearing. Pet. Ex. 47; Pet. Ex. 80.

i. Dr. Byers' Reports

Dr. Byers explained that the pathophysiology of MS has recently improved with MS patterns separated into four subtypes. Patterns I and II are proposed to be autoimmune mediated characterized by perivascular T cell, macrophage infiltration, and demyelination of the nerves. Pet.

⁴⁶ B. Hakiki et al., 'Subclinical MS': Follow-up of Four Cases, 15 EUR. J. OF NEUROLOGY 858 (2008), filed as "Pet. Ex. 25."

⁴⁷ Antonio Carlos Martins Maia Jr. et al., *Incidental Demyelinating Inflammatory Lesions in Asymptomatic Patients: A Brazilian Cohort with Radiologically Isolated Syndrome and a Critical Review of Current Literature*, 70 ARQUIVOS DE NEURO-PSIQUIATRIA 5 (2012), filed as "Pet. Ex. 30."

⁴⁸ JI O'Riordan et al., *Asymptomatic Spinal Cord Lesions in Clinically Isolated Optic Nerve, Brain Stem, and Spinal Cord Syndromes Suggestive of Demyelination*, 64 J. OF NEUROLOGY, NEUROSURGERY & PSYCHIATRY 353 (1998), filed as "Pet. Ex. 34."

Ex. 47 at 2-3; Pet. Ex. 62.⁴⁹ Patterns I and II differ in that pattern II has a more prominent deposition of IgG and complement at sites of active myelin destruction. These two patterns are seen in relapsing remitting MS and have been studied in EAE animal models where disease is induced by injecting myelin oligodendrocyte glycoprotein (“MOG”) into the animal. Pet. Ex. 47 at 2-3. Quiescent lesions can be reactivated within hours by the induction of inflammation. *Id.* at 3; Pet. Ex. 107.⁵⁰ Patterns III and IV have distinct appearance with no demyelination. Pet. Ex. 47 at 3; Pet. Ex. 67.⁵¹

Dr. Byers then explained immunologically how a vaccine can induce TM/MS relapse through cytokine response and can do so quickly. Pet. Ex. 47 at 3-4, 5. She explained that cytokines produced in the periphery and released through inflammation can cross the blood brain barrier, activate astrocytes and microglial cells which then produce more cytokines, primarily IL-6 and IL-17, which can cause demyelination of axons and apoptotic death of oligodendrocytes (the cells in the brain that produce and maintain the myelin that coats the axons and feeds the neurons). *Id.* at 3. The tissue destruction activates more immune reactive cells causing further damage to the nerves and producing more inflammation. *Id.*; Pet. Ex. 60.⁵² The IL-6 produced by macrophages, dendritic cells, and mast cells in the innate immune system differentiates TH17 cells which are cytotoxic to myelin containing cells. Pet. Ex. 47 at 4.⁵³ IL-6 itself can produce inflammation, demyelination, and axonal damage. *Id.* “Even a small population of IL-17 producing cells invading the CNS could induce potent astrocyte activation with resultant toxic levels of IL-6 thereby accounting for the IL-6 mediated cascade leading to destructive and disabling pathology.” *Id.*

Dr. Byers cited *Kaplin et al.*, which found that IL-6 was elevated in the cerebrospinal fluid (“CSF”) of TM patients during flares. Pet. Ex. 80 at 4; Pet. Ex. 27.⁵⁴ *Graber et al.*, citing *Miljkovic et al.* 2002,⁵⁵ also reported increased IL-6 in the CSF of both TM and MS patients. Pet. Ex. 80 at 3. *Petkovic & Castellano* added that IL-6 has also been found to prevent removal of the destroyed myelin, which impairs remyelination of the neurons. Pet. Ex. 80 at 4; Pet. Ex. 67.⁵⁶ Further, it was recently found that TH17 cells and IL-17 (the cytokine produced by TH17 cells) levels were higher in active MS lesions than in inactive areas, although TH17 cells were present in both. IL-17, along with T cells, was also expressed on astrocytes and oligodendrocytes. Pet. Ex. 80 at 1-2, 4.⁵⁷ *Graber et al.* also demonstrated that IL-17 producing cells invade the CNS and produce IL-6, which is toxic to the brain. Pet. Ex. 80 at 3; Pet. Ex. 60.⁵⁸ Reactive astrocytes previously thought to be responsible for glial scarring are now considered to be early actors in lesions. Pet. Ex. 80 at 2.

⁴⁹ Claudia Lucchinetti, MD et al., *Heterogeneity of Multiple Sclerosis Lesions: Implications for the Pathogenesis of Demyelination*, 47 ANNALS OF NEUROLOGY 707 (2000), filed as “Pet. Ex. 62.”

⁵⁰ Serres et al., *supra* note 43.

⁵¹ Filip Petković, Ph.D. & Bernardo Castellano, *The Role of Interleukin-6 in Central Nervous System Demyelination*, 11 NEURAL REGENERATION RES. 1922 (2016), filed as “Pet. Ex. 67.”

⁵² Jerome J. Gruber et al., *Interleukin-17 in Transverse Myelitis and Multiple Sclerosis*, 19 J. OF NEUROIMMUNOLOGY 124 (2008), filed as “Pet. Ex. 24” and “Pet. Ex. 60.”

⁵³ It appears that the *Janssens et al.* 2015 article Dr. Byers relied upon to support this statement was not filed.

⁵⁴ Kaplin et al., *supra* note 27.

⁵⁵ This article was not filed.

⁵⁶ Petković & Castellano, *supra* note 51.

⁵⁷ Based on review of the record, it does not appear that the *Tzartos et al.* 2008 article Dr. Byers relied upon to support this statement was filed.

⁵⁸ Gruber et al., *supra* note 52.

Astrocytes in inactive lesions can be activated by TNF- α and IL-1 β , the cytokines released during peripheral inflammation from infections or vaccines. *Id.*⁵⁹ Cultured human astrocytes were found to have increased IL-6 production after stimulation. Pet. Ex. 80 at 3; Pet. Ex. 60.⁶⁰ These “flares” have been seen in animal models and occur either directly by generic response to cell bacterial cell-wall products or indirectly by secondary enhancement of an overactive immune response, leading to bystander activation or an MS specific immune pathway. Regardless, both pathways are initially dependent on activation of the innate immune system. Pet. Ex. 47 at 3; Pet. Ex. 107.⁶¹

Thus, Dr. Byers stated that the literature supports that both IL-6 and IL-17 are increased in the peripheral blood mononuclear cells in TM and early MS and induce astrocyte IL-6 production. Pet. Ex. 8-0 at 4; Pet. Ex. 60.⁶² IL-17 is a crucial proinflammatory cytokine that induces TNF- α and chemokines, attracts neutrophils, and enhances maturation of dendritic cells. *Id.*⁶³ *see also* Pet. Ex. 47 at 3-4; Pet. Ex. 107 at 2.⁶⁴ Finally, IL-6 is produced within hours of vaccine administration and “can push anti-myelin basic protein specific CD17+ cells to maturation and differentiation.” Pet. Ex. 80 at 1-2.⁶⁵

Dr. Byers submitted that it is now well accepted that the innate immune system has memory and will react with specificity and intensity. Pet. Ex. 47 at 5; Pet. Ex. 64.⁶⁶ *Sun et al.* stated that natural killer (“NK”) cells, which are often designated as part of the innate immune system, “have been shown to demonstrate both specificity and memory against a wide range of antigens [] and stimuli”, including pro-inflammatory cytokines. Pet. Ex. 72.⁶⁷

Dr. Byers added that pertussis toxin in combination with PLP and incomplete Freund’s adjuvant is widely used in animal studies as an adjuvant to produce PLP-specific IL-17 producing CD4+ cells in the periphery to induce EAE. Pet. Ex. 80 at 2. “Therefore, stimulation of the innate immune system with unrelated environmental pathogens can drive the adaptive immune system toward TH17 differentiation, which in turn can support organ-specific autoimmunity provided that the organism is genetically prone for the development of autoimmunity.” *Id.*⁶⁸

Dr. Byers agreed with Dr. Kinsbourne that the innate immune system is capable of an anamnestic response. Pet. Ex. 47 at 5.

⁵⁹ Based on review of the record, it does not appear that the *Ponath et al.* 2018 article Dr. Byers relied upon to support this statement was filed.

⁶⁰ Gruber et al., *supra* note 52.

⁶¹ Serres et al., *supra* note 43.

⁶² Gruber et al., *supra* note 52.

⁶³ *Supra* note 53.

⁶⁴ Serres et al. studied the association between microbial infection and potential reactivation of MS lesions in rats finding at least in part, the ability of quiescent MS lesions to rapidly reinitiate the cell recruitment processes in the rats through a pattern type I delayed type hypersensitivity response showing systemic infection can alter the pathogenesis of MS like lesions regardless of the lesions’ etiology. Pet. Ex. 107 at 4820, 4825-26, *supra* note 43.

⁶⁵ The *Serada et al.* 2008 article Dr. Byers relied upon to support this statement was not filed.

⁶⁶ Timothy E. O’Sullivan et al., *Natural Killer Cell Memory*, 43 IMMUNITY 634 (2015), filed as “Pet. Ex. 64.”

⁶⁷ Joseph C. Sun et al., *Immunological Memory Within the Innate Immune System*, 33 THE EMBO J. 1295 (2014), filed as “Pet. Ex. 72.”

⁶⁸ Dr. Byers quoted Gold & Luhder 2008, which was not filed.

ii. Dr. Byers' Testimony

At hearing, Dr. Byers deferred to Dr. Kinsbourne on neurological issues, stating her only function in this case was to explain petitioner's onset of symptoms within 24 hours of receipt of the Tdap vaccine. Tr. 128, 135.

Dr. Byers agreed that the literature and animal studies support the theory that vaccinations, like infections, can cause MS relapse because both are foreign antigens and vaccinations by nature are meant to mimic infection. Tr. 118.

Dr. Byers stated that within 24 hours of the Tdap vaccine, petitioner's innate immune system produced cytokines that activated a quiescent lesion in her thoracic spine. Tr. 135. Literature and animal models demonstrate that the innate immune system can cause an MS relapse within a day of exposure to a vaccine antigen. Tr. 119. She explained that both innate and adaptive immune systems involve T cells. Tr. 136-37. The innate immune system reacts very quickly, within four hours. Tr. 122-23. Innate immune T cells created from systemic stimulation can start in the periphery and move to various organs, including but not limited to the brain. Tr. 138. The role of a vaccine is to initiate the adaptive immune system by initially activating the innate immune system. Tr. 152.

Dr. Byers stated that the prior controversy of whether cytokines could breach the blood brain barrier ended and it is now known that the CNS contains certain cells that are activated by astrocytes after systemic stimulation. Tr. 122-23, 144-45; Pet. Ex. 60.⁶⁹ *Graber et al.* showed that IL-17 regulates the secretion of TNF-alpha, TNF-beta, and IL-6 astrocytes in the brain. Dr. Byers noted this was an in-vitro study conducted in a dish not on animals or humans. Tr. 144-45.

Dr. Byers discussed the use of MOG as a glycoprotein to induce MS in animal studies for over 40 years. Tr. 157-58. In *Serres et al.*, animals were injected with MOG then cytokines to reproduce MS lesions. Once the lesions healed, the animals were injected with lipopolysaccharide to induce prolonged systemic inflammation. This caused the lesions to flare, inducing EAE. Tr. 120-24, 157-58; Pet. Ex. 107.⁷⁰ MRIs demonstrated that "[a]fter LPS injection, new recruitment of inflammatory cells and decreased demyelination were evident, with close spatial correlation, in the lesioned corpus callosum' within 24 hours after the injection." Tr. 122; Pet. Ex. 107 at 5. The evidence suggested that infectious diseases more than likely activate disease activity in MS, "either directly by the generic response to cell bacterial cell-wall products (LPS and analogs) or indirectly via secondary enhancement of an overactive immune response, leading to bystander activation." Tr. 124; Pet. Ex. 107 at 7-8.

Dr. Byers added that in *Fernandez et al.*, healthy individuals were given a single subcutaneous dose of tetanus toxoid with blood samples drawn immediately before vaccination and then again nine weeks later. Tr. 147-49; Pet. Ex. 101 at 1809.⁷¹ Cytokines measured 9 weeks following vaccination included IL-2, IFN-gamma, TNF-beta and IL-4, which are produced by the

⁶⁹ *Graber et al.*, *supra* note 52.

⁷⁰ *Serres et al.*, *supra* note 43.

⁷¹ *Fernandez et al.*, *supra* note 19.

adaptive immune system. She added that these cytokines can be produced by the innate immune system but are not exclusively in the innate immune system. Tr. 150-51; Pet. Ex. 101 at 1810, 1812.

Dr. Byers acknowledged that in *Kashiwagi et al.*, it was unknown if cytokines were present in the actual subjects because it was an in vitro study where T-lymphocytes were extracted from vaccinated people then examined for IL-1beta, IL-4, IL-6, IL-12, gamma interferon, and TNF-alpha. Tr. 151-52; Pet. Ex. 106.⁷² Further, most of the patients received the PCV7 vaccine. Tr. 153. Only two patients received the Tdap vaccine. Tr. 153-54; Pet. Ex. 106 at 678. Further, *Kashiwagi et al.* discussed type one interferons and inflammatory cytokines enhancing the expression of costimulatory molecules to help the recognition of T cell signals; it did not discuss vaccines affecting the central nervous system. Tr. 155.

Dr. Byers acknowledged that *Buljevac et al.* did not discuss vaccines either, but it showed that infection can exacerbate MS and the probability of that occurring. Tr. 146-47; Pet. Ex. 99 at 955.⁷³ She conceded that *Barnett & Prineas* discussed a rare form of lesions not involved here but submitted it to show exacerbation of MS lesions after respiratory infection. Tr. 138, 141-44; Pet. Ex. 47 at 5; Pet. Ex. 105 at 460-61.⁷⁴

Dr. Byers summarized that reactivation of inactive lesions is the result of innate cytokine activation of cells—namely macrophages, T cells, and B cells—that already exist in the quiescent lesions. Tr. 162. Each of these cells can cause demyelination by producing damage to neurons and are characteristic of MS. Tr. 162-63. Once activated, they light up with gadolinium. This was shown here on the August 2013 MRI with an area of hyperintensity on the thoracic spine at T6-T7. Tr. 162. Dr. Kinsbourne confirmed the lesions were in the appropriate place to explain petitioner’s symptoms. Tr. 162-63.

Dr. Byers concluded that petitioner had preexisting lesions in the thoracic spine that were activated by the Tdap vaccination and were responsible for the clinical symptoms she experienced. The temporal relationship between the vaccination and the onset of her symptoms, along with the MRIs, supported the flare of a single lesion. Tr. 125-27.

c. Respondent’s Expert, Dr. Subramaniam Sriram

Dr. Sriram obtained his M.B., B.S. from the University of Madras in India in 1973. Resp. Ex. B. He is board certified in internal medicine, as well as psychiatry and neurology. *Id.* at 1. He has held several academic positions at Stanford University, the University of Vermont, and Vanderbilt University where he currently teaches. *Id.* at 1-2. At hearing, Dr. Sriram described his involvement in clinical trials of MS as a principal investigator or sub-investigator, with at least 10-12 clinical trials ongoing in his division. Tr. 171. He also does research on MRI measurements

⁷² Kashiwagi et al., *supra* note 26.

⁷³ Buljevac et al., *supra* note 17.

⁷⁴ Michael H. Barnett, MBBS & John W. Prineas, MBBS et al., *Relapsing and Remitting Multiple Sclerosis: Pathology of the Newly Forming Lesion*, 55 ANNALS OF NEUROLOGY 458 (2004), filed as “Pet. Ex. 58” and “Pet. Ex. 105.”

especially of the spinal cord in patients with progressive MS. He works in collaboration with Vanderbilt but conducts the studies in his own clinical laboratory on the mechanism of how nerves get demyelinated and recover from demyelinating injuries. Tr. 171. Two-thirds of his peer-reviewed publications are on MS or MS related issues. Tr. 171-72. He has authored 4-5 papers on MRIs in MS patients. Tr. 172. He testifies for Health & Human Services in vaccine cases and has for about 12 years. He does not testify outside of the Program. Tr. 172.

Dr. Sriram's credentials were stipulated to, and he was qualified as an expert in neurology and neuroimmunology. Tr. 165. Dr. Sriram discussed his current positions and his treatment of about 1200 MS patients a year at Vanderbilt. Tr. 170. He reads 10-15 MRIs per week. He has never treated a patient whose MS was caused by a vaccine. Tr. 170.

Dr. Sriram submitted four reports in this case and testified at hearing. Resp. Ex. A; Resp. Ex. J; Resp. Ex. K; Resp. Ex. L. Most of Dr. Sriram's opinions focused on refuting the notion that the Tdap vaccine can cause MS or could do so in one day.

i. Dr. Sriram's First Report

In his first report, Dr. Sriram agreed petitioner has RRMS and with the criteria for diagnosing MS set forth by Dr. Kinsbourne. Resp. Ex. A at 2-3; Resp. Ex. C at 1.⁷⁵ Dr. Sriram wrote that petitioner had non-enhancing lesions in the brain, including a T1 hypointense lesion meaning at least 6 months old. Resp. Ex. A at 3; Pet. Ex. 4 at 13. Follow up MRIs in December 2013 showed at least two non-enhancing lesions in the cervical spine. Resp. Ex. A at 3; Pet. Ex. 6 at 10. Her clinical symptoms and radiological signs were consistent with MS. Resp. Ex A at 3.

Dr. Sriram argued that Tdap vaccine has been shown to be "modestly protective in the development of MS." Resp. Ex. A at 3; Resp. Ex. E;⁷⁶ Resp. Ex. F.⁷⁷ He agreed the cause of MS is unknown but is hypothesized to be autoimmune, though evidence of an autoantigen is lacking. Resp. Ex. A at 3. He agreed that acute worsening of MS is sometimes preceded by infection, but infection is not thought to be a cause of MS. *Id.* "To this end, it has been suggested that MS can be triggered by a vaccine," however vaccines are recommended for those with MS and no literature exists to support vaccines worsening MS. Resp. Ex. A at 3-4; Resp. Ex. G.⁷⁸

Dr. Sriram opined that petitioner's development of symptoms in less than a day after the Tdap vaccine was too short "for a biological basis for immune response". Resp. Ex. A at 4. The prevailing view for development of relapses of MS is activation of autoreactive T cells—which are a prominent component of immunological injury in MS—that migrate to the CNS and react to antigens present on myelin membranes. *Id.*; Resp. Ex. H.⁷⁹ "For the requisite T cells to cause

⁷⁵ Chris H. Polman, MD, PhD et al., *Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria*, 69 ANNALS OF NEUROLOGY 292 (2011), filed as "Resp. Ex. C."

⁷⁶ DeStefano et al., *supra* note 33.

⁷⁷ Mailand & Frederiksen, *supra* note 34.

⁷⁸ Olivier T. Rutschmann, MD, MPH et al., *Immunizations and MS: A Summary of Published Evidence and Recommendations*, 59 NEUROLOGY 1837 (2002), filed as "Resp. Ex. G."

⁷⁹ Elliot M. Frohman, M.D., Ph.D. et al., *Multiple Sclerosis – The Plaque and Its Pathogenesis*, 354 N. ENG. J. MED. 942 (2006), filed as "Resp. Ex. H."

pathological symptoms, the lymphocytes would need to be activated, proliferate and then traffic to the nervous system.” Resp. Ex. A at 4. Activation and proliferation of T cells takes more than 24 hours. His own studies of demyelination in animals show it usually takes 7-14 days. *Id.*; Resp. Ex. I.⁸⁰ “The doubling time of T cells is approximately 24-48 hours, a time frame under which antigen reactive T cells are not likely to expand and migrate to the spinal cord.” Resp. Ex. A at 4. Therefore, it was highly unlikely that an immune response which triggered RRMS was activated in one day. *Id.*

Dr. Sriram disagreed that petitioner had an anamnestic response to the vaccine because those are seen in antibody mediated diseases like allergy disorders. Further, the development of an innate immune response cannot cause a T cell mediated autoimmune reaction, and MS is a T cell mediated autoimmune disease. Resp. Ex. A at 4. Therefore, petitioner’s Tdap vaccine did not contribute to her development of RRMS. *Id.* at 5.

ii. Dr. Sriram’s Second Report

In his second report, Dr. Sriram “disagree[d] with all [Dr. Byers’] statements...” Resp. Ex. J at 1. He disagreed that IL-6 and IL-17 cause demyelination and apoptotic death of oligodendrocytes. Resp. Ex. J at 2. A “[c]areful reading of [Graber *et al.*] shows that IL-17 could not even be detected in cerebrospinal fluid of patients with MS.” *Id.* (emphasis in original); Pet. Ex. 60.⁸¹ Petkovic & Castellano studied demyelination following overexpression of IL-6 in the brains of mice with no support for IL-6 causing demyelination, refuting Dr. Byers’ argument that IL-6 is responsible for demyelination. Resp. Ex. J at 2-3; Pet. Ex. 67.⁸² Oligodendrocytes are not feeding stations for axons or neurons, therefore Dr. Byers’ opinion that “oligodendrocytes also feed the neurons, providing them with the appropriate nourishment required” shows a lack of understanding of the function of oligodendrocytes. Resp. Ex. J at 2. Finally, the presence of cytokines found in MS lesions does not imply that cytokines cause demyelination, and this theory is unsupported by literature. *Id.*

Further, Dr. Byers’ reliance on *Graber et al.* and *Kashiwagi et al.* to support a 24-hour onset was erroneous. The children studied in *Kashiwagi et al.* received DPT—not Tdap like petitioner received. Resp. Ex. J at 3; Pet. Ex. 106.⁸³ The innate immune response was most likely driven by the bacterial product present in the DPT, the old whole cell pertussis vaccine. No data exists on the role adjuvants play in the Tdap vaccine to induce innate immunity. Resp. Ex. J at 3.

Dr. Sriram disagreed with Dr. Byers’ reliance on *O’Sullivan et al.* because the authors studied NK cells, which have nothing to do with MS. Resp. Ex. J at 3-4; Pet. Ex. 64.⁸⁴ Regardless, Dr. Byers failed to explain how NK cells can be activated in less than 24 hours. *Id.*

⁸⁰ Caigan Du et al., *Administration of Dehydroepiandrosterone Suppresses Experimental Allergic Encephalomyelitis in SJL/J Mice*, 167 THE J. OF IMMUNOLOGY 7094 (2001), filed as “Resp. Ex. I.”

⁸¹ Gruber et al., *supra* note 52.

⁸² Petković & Castellano, *supra* note 51.

⁸³ Kashiwagi et al., *supra* note 26.

⁸⁴ O’Sullivan et al., *supra* note 66.

Dr. Sriram concluded that “[n]one of the statements made by Dr. Byers is supported by scientific evidence.” Resp. Ex. J at 4. There is no evidence that the Tdap vaccine causes peripheral inflammation; that cytokines cause demyelination in MS; that activation of the innate immune system by Tdap causes the release of IL-17; that cytokines cross the BBB activating astrocytes to produce IL-6; that the resulting production of hydrogen peroxide causes demyelination; or that oligodendrocytes act to provide nutritional support. *Id.* at 4-5. Further, the idea that an innate immune response is harmful to the CNS and causes demyelination reflects a “misunderstanding of causality.” *Id.* at 5. Activation of the innate immune system is neuroprotective and reduces inflammation. This is because many of the inducers of innate immunity are mediated by activation of bacterial and viral cell and nucleic acid products, which activate class I interferons and TNF alpha which is why interferon medications are used to treat MS. *Id.* TNF, one of the main products of innate immunity, is unlikely to cause demyelination, as evidenced by worsening inflammation in prior attempts to treat MS patients with anti TNF antibodies. *Id.*; Resp. Ex. P.⁸⁵

Succinctly, Dr. Sriram concluded Tdap causing the expansion of cytokines which in turn cause demyelination within 24 hours is unsupported by the literature and disregards the protective role “of potent innate immunity driving vaccines in protecting from the development of MS. Tetanus toxoid vaccines have been shown to reduce the development of MS.” Resp. Ex. J at 5; Resp. Ex. Q;⁸⁶ Resp. Ex. R.⁸⁷

iii. Dr. Sriram’s Third Report

In his third report, Dr. Sriram maintained that amplification of the innate immune system in less than one day following Tdap vaccination is unsupported. Resp. Ex. K at 1. Further, there is no support that the Tdap vaccine can trigger an anamnestic response and acute relapse of MS. *Id.*

Dr. Sriram disagreed that infections and vaccinations are equivalent. Tdap vaccine does not contain any live, attenuated organism or antigen capable of causing infection. Resp. Ex. K at 2. He agreed his own studies propose the role of infections in MS relapse, but they do not propose vaccines as a trigger for MS since the cause of MS relapse is unknown. He disagreed that the literature supports infectious antigens as inducers of relapses in MS. *Id.*; Pet. Ex. 53.⁸⁸

Dr. Sriram further disagreed with Dr. Kinsbourne that simply because no other antecedent cause exists, the vaccine is the trigger. Temporal relationship is not a “valid scientific methodology to ensure a causal connection.” Resp. Ex. K at 2.

⁸⁵ L.S. Group, *TNF Neutralization in MS: Results of a Randomized, Placebo-controlled Multicenter Study: The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group*, 53 NEUROLOGY 457 (1999). Presumably by mistake, both this article and another were filed as “Resp. Ex. Q.” Thus, for clarity, this article will be referred to as “Resp. Ex. P.”

⁸⁶ Ellen Bible, *Disease Activity is Reduced in CIS After BCG Vaccination*, 10 NATURE REV. NEUROLOGY 62 (2014), filed as “Resp. Ex. Q.”

⁸⁷ Mauricio F. Farez & Jorge Correale, *Immunizations and Risk of Multiple Sclerosis: Systematic Review and Meta-analysis*, 258 J. OF NEUROLOGY 1197 (2011), filed as “Resp. Ex. R.”

⁸⁸ Shoenfeld, *supra* note 18.

Dr. Sriram concluded that neither Drs. Kinsbourne nor Byers provided a biological process by which a Tdap vaccine can induce an MS relapse through activation of the innate immune system. Resp. Ex. K at 2. More specifically, no evidence exists that shows that relapses in MS are mediated exclusively by activation of innate immune pathways; that a cytokine “storm” induced by the Tdap vaccine in less than 24 hours can target the CNS without causing any systemic side effects; that cytokines cause demyelination; or that Tdap vaccines can induce the kind of cytokines suggested by petitioner’s experts as responsible for clinical relapse. *Id.* at 2-3.

i. Dr. Sriram’s Fourth Report

Dr. Sriram’s fourth report focused on petitioner’s MRIs taken in August 2013 and December 2013 to show that her MS predated the July 12, 2013 Tdap vaccine. Resp. Ex. L at 1.

Dr. Sriram explained the development of demyelinating lesions which initially appear as enhanced when gadolinium is administered and represent acute inflammation. Lesions can enhance for more than 12 weeks. Resp. Ex. L at 1. Further, brain lesions are identified by magnetic pulse sequences as T1, T2, and T2 flair. *Id.* at 2. “Since the basic underpinnings of magnetic sequence is the polarity of hydrogen atoms and because water is the most abundant source of hydrogen in tissue, these sequences provide a biomarker of the underlying pathology.” *Id.* Dark lesions are considered hypointense and T1 hypointensity reflects structural change; brighter lesions are considered hyperintense and T1 hyperintensity reflects inflammation and swelling.⁸⁹ *Id.* Over time, enhancement resolves but the evolution of T1 hypointensity is variable, with some becoming undetectable while others persist. Lesions that persist in excess of 3 months after resolution of enhancement are referred to as black holes. *Id.*

Dr. Sriram calculated the volume of the brain lesions present on the August 28, 2013 MRI pursuant to *Cotton et al.*, and he concluded that the duration of the right parieto-occipital lesion alone was about 12 weeks old or began around June 5, 2013 prior to the Tdap vaccine. Resp. Ex. L at 2-3; Resp. Ex. M.⁹⁰ This T1 hypointense lesion persisted and was seen on the December 2013 MRI, suggesting the lesion became a black hole. *Id.* at 4. There is a 75% probability that a black hole seen for 4 months would have been enhancing for at least 8 weeks, therefore the beginning of the enhancement would predate the vaccine. *Id.* at 4-5; Resp. Ex. N.⁹¹

Based on the foregoing calculation of the duration of petitioner’s brain lesion, Dr. Sriram argued that the lesions could not have developed following the vaccination. Further, the biological process of demyelination could not occur within 24 hours. Resp. Ex. L at 5.

⁸⁹ This was written incorrectly in the report as both being hypointense.

⁹⁰ Francois Cotton, MD et al., *MRI Contrast Uptake in New Lesions in Relapsing-Remitting MS Followed at Weekly Intervals*, 60 NEUROLOGY 640 (2003), filed as “Pet. Ex. 19” and “Resp. Ex. M.”

⁹¹ Francesca Bagnato et al., *Evolution of T1 Black Holes in Patients with Multiple Sclerosis Imaged Monthly for 4 Years*, 126 BRAIN 1782 (2003), filed as “Resp. Ex. N.”

ii. Dr. Sriram's Testimony

Dr. Sriram agreed petitioner has RRMS, a clinical syndrome characterized by episodic deficits of neurological dysfunction primarily affecting the optic nerves, brain stem, or spinal cord. Tr. 174. The events of neurological deficits have an onset, progression, and resolution. In between events, the patient may be asymptomatic or minimally symptomatic. The episodes are referred to as relapses. Tr. 174, 221-22.

Dr. Sriram explained that MS is an autoimmune response characterized by autoreactive T cells to an unknown central nervous system antigen and is an adaptive immune response. Tr. 174. While immune T cells are the primary drivers, CD-4 T cells and CD-8 T cells have recently been thought to act independently or conjointly in developing demyelinating lesions but how the final event happens is conjecture. Tr. 175. Autopsies show adaptive immune cells primarily in the brains of those who die from MS. Tr. 175. An adaptive immune response takes 2-3 weeks in a naïve person and in those with relapsing/remitting MS. Tr. 175-76. Almost all medications currently used in treating patients with MS reduce the activity of T cells and B cells, using the innate immune cytokine. Tr. 176. There is no evidence in this case that petitioner's innate immune response caused her RRMS. Tr. 176.

Dr. Sriram stated there is no known cause for MS or MS relapses and nothing in the literature exists to support that a Tdap vaccine can cause MS or MS relapses. Tr. 205, 109, 210. Further, there is no reliable evidence that either the innate immune system alone or the adaptive immune system can drive an MS relapse within 24 hours. Tr. 210. Therefore, the Tdap vaccine petitioner received did not cause her RRMS. Tr. 212.

Dr. Sriram disagreed that a Tdap vaccine could trigger MS. Tr. 188, 221-22, 226. He agreed that upper respiratory and/or gastrointestinal infections can cause relapses in MS, presumably from some form of immune process like molecular mimicry. But the cause of MS has not been proven, and nothing in the literature or epidemiological studies supports an immune response to a vaccine as pathogenic. Tr. 222-23, 238-39. The literature relied on by Dr. Kinsbourne discusses replicating viruses or bacteria; vaccines that contain a toxoid do not replicate like infection. Therefore, vaccines and infections are not the same. Tr. 188-89, 200. A toxoid contains denatured proteins modified to be non-toxic. It does not contain a replicating attenuated organism necessary to trigger an event. Tr. 188-89, 199-200.

Further, "tetanus toxoid doesn't induce an innate immune response because the body does not recognize this as a foreign pathogen. It goes through an adaptive immune response because it's a foreign protein and you develop an antibody and T cell response...that takes about 14 days for an adaptive immune response to occur if one is not primed and perhaps sooner if one is primed." Tr. 233-34. When you receive a Tdap for the first time, the response in developing antigenic toxoid antibodies takes between 2-3 weeks. If you have received Tdap in the past and are primed or have antibodies, an antibody response will take about 7 days. Tr. 204. This is because an injection into the deltoid muscle takes time to drain into the regional lymph nodes where it activates lymphocytes. Tr. 204. The lymphocytes must divide which takes about one day. Tr. 204. Next, the cells leave the lymph nodes and travel all over the body, some go to the brain where they would

have to cross the BBB and become activated in such a way as to cause an inflammatory response. Tr. 204-05, 234-35. This process would take at least 5-6 days. Tr. 234. The onset here is too quick to assume the tetanus toxoid resulted in an adaptive response that caused demyelination in the brain. Tr. 234-35.

Dr. Sriram agreed vaccines can cause a hypersensitivity response, but it is usually due to the adjuvants used to amplify the immune response, not the toxoid alone. Tr. 200. However, even if petitioner had an abnormal response to the Tdap vaccine, he would still question the process that connected the tetanus toxoid to increased demyelination or inflammation in the brain. Tr. 200-01. Dr. Sriram stated he was unclear what petitioner's theory was or the "process by which you get this big, humongous recruitment of lymphocytes into the brain and amplification of it and the damage thereof" from a protein injected into the deltoid muscle. Tr. 202.

Petitioner's counsel clarified for Dr. Sriram that petitioner's theory did not include the content of the Tdap vaccine or that the Tdap caused MS lesions but rather that the inflammatory response to her receipt of the Tdap triggered the onset of symptoms in a person with pre-existing or multiple pre-existing MS lesions that were present but asymptomatic. Tr. 235-36, 248. Dr. Sriram disagreed that any evidence exists that supports a Tdap vaccine causing such a systemic response. Tr. 236. He agreed vaccines cause an immune response with some degree of inflammation regionally in the lymph nodes after vaccination. Tr. 241-42. He also agreed there is an increase in cytokines in 24 or 48 hours after vaccination but not a "massive increase" of cytokines sufficient to cause demyelination. Tr. 237. He explained that live vaccines can cause a systemic response which includes fevers, chills, body aches, and pain because an attenuated bug is introduced to the body. Tr. 243. He agreed that sometimes the adjuvant used to amplify the immune response can produce some degree of inflammation usually at the site of the injection, but vaccines do not result in pathogenic illness. Tr. 243-44. He then stated that whether live or attenuated, a vaccine drives an innate immune response which is the reason for the systemic effect. Tr. 245-46. He explained that the innate immune system is a mechanism by which the body gets ready to fight, whether an attenuated or heat killed virus vaccine is injected, the body recognizes a foreign pathogen, and the receptors mount an inflammatory response to get rid of it, even though it is a dead virus, the body does not know that. He was unsure whether the acellular pertussis has an innate immune receptor. Tr. 246. He agreed if petitioner had the Tdap vaccine before, the response would be quicker; but he referred to *Fernandez et al.* to show that the timing of an immune response would depend on when the prior Tdap was received. Tr. 246-47; Pet. Ex. 101.⁹² Further, he pointed out that petitioner did not report any local reaction to her vaccine, so if she had an inflammatory response, it was mild. Tr. 244.

Dr. Sriram maintained that no clear evidence exists of which cytokines are pathogenic in MS. Tr. 209. Most of what is known about the pathogenesis of MS comes from in vitro testing, which involves putting cytokines in a petri dish with myelin forming cells to see which causes damage to the myelin forming cells. No relationship between severity, chronicity, or appearance of illnesses with any of these cytokines has been seen in MS patients. Tr. 209-10.

⁹² Fernandez et al., *supra* note 19.

Dr. Sriram discussed some of the literature relied on by petitioner. Tr. 176-77. *Graber et al.* was an in vitro study where T cells were stimulated in petri dishes with blood/lymphocytes from healthy patients, those who relapsed or recovered from relapse, and those with TM. Tr. 177; Pet. Ex. 60.⁹³ Cytokines—specifically IL-17 and IL-6—secreted by the T cells were studied with no statistical difference in IL-17 levels found between MS patients and the healthy controls; a statistical difference was found between TM patients and the control subjects. Tr. 178; Pet Ex. 60 at 27.

Kashiwagi et al. studied healthy children two months to seven years of age, some with respiratory infections, who received regularly scheduled vaccines. Tr. 206-08; Pet. Ex. 106.⁹⁴ Lymphocytes were taken from the periphery of these children and stimulated in petri dishes with various vaccine antigens, including DPT, Hib, and pneumococcal antigens. Tr. 207. Various combinations were studied to find which vaccines caused the highest amount of cytokine release. Most cytokine levels were found to be higher than in unvaccinated children. IL-1beta, TNF, and G-CSF were the lowest in DPT, and IL-6 was slightly increased in DPT although the difference was minimal. Tr. 207. *Kashiwagi et al.* did not support the idea that cytokines produced from vaccination can negatively impact the CNS. Tr. 208-09. Dr. Sriram added that *Kashiwagi et al.* studied DTP vaccine, and he did not believe Tdap and DTaP are the same; Tdap has a higher concentration of tetanus toxoid while DTaP has more pertussis. Tr. 241.

Dr. Sriram added that in studies where T-lymphocytes are activated by MOG or MBP injected into mice, it takes three to four days for the mice to get sick and show paralysis. Tr. 202-03. Thus, petitioner's theory that the immune response could occur within 24 hours is not persuasive. Tr. 202-03. Dr. Sriram agreed that hypersensitivity reactions occur within hours, but an adaptive response triggering demyelination takes more time. Tr. 203.

Dr. Sriram stated that *Hapfelmeier et al.* was the largest case-controlled study done on the relationship between vaccination and MS and involved 12,000 patients and 17,000 controls. Tr. 191; Resp. Ex. S.⁹⁵ The study showed vaccines, specifically the Tdap vaccine, delayed or reduced the susceptibility of MS. Tr. 191-94. Acknowledging the flaws in the study, Dr. Sriram explained that epidemiological studies will always have some limitations, but the limitations are offset by the fact that there are so many patients in an epidemiologic study. Tr. 195. *DeStefano et al.* found similar results, but on a smaller scale. Tr. 194; Resp. Ex. E.⁹⁶ "So all these vaccines not only – for some reason or the other that we don't understand have what we call off-targeted effects. They...clearly prevent tetanus from happening, prevent influenza from happening, but they also for some reason are able to reduce the incidence of multiple sclerosis." Tr. 194.

Dr. Sriram referenced *Rutschmann et al.*, a compendium of all the papers in existence at the time, which found that "tetanus vaccine does not increase the risk of relapses in patients with MS." Tr. 196-97; Resp. Ex. G.⁹⁷

⁹³ *Graber et al.*, *supra* note 52.

⁹⁴ *Kashiwagi et al.*, *supra* note 26.

⁹⁵ *Hapfelmeier et al.*, *supra* note 45.

⁹⁶ *DeStefano et al.*, *supra* note 33.

⁹⁷ *Rutschmann et al.*, *supra* note 78.

Dr. Sriram also discussed petitioner's MRI findings and *Cotton et al.*, as setting the criteria for MS lesions. Dr. Sriram stated there are three main signals for MS lesions: T1, T2, and T1 post gadolinium ("gad"). Tr. 179. Patients with an acute lesion have T1 enhancement and T1 post-gad positive, as seen on petitioner's August 2013 MRI. Tr. 179-80; Resp. Ex. M.⁹⁸ T2 lesions are previously T1 enhanced lesions. Tr. 180. Dr. Sriram claimed that MRI studies show when a lesion developed, how long it has stayed, and what is going to happen later. Tr. 180. However, he admitted that without any prior MRI studies, it would be impossible to tell whether a lesion is an old lesion that re-enhanced or a new enhancing lesion. Tr. 180-81. This is particularly true of spinal cord lesions because they are confined to a small area and are harder to read. Tr. 181.

As discussed in his report, Dr. Sriram explained that the lesions seen on petitioner's brain MRI preceded the vaccine based on their size and duration of enhancement. Tr. 182-83. While admitting that spinal cord lesions are more difficult to measure, he estimated that the thoracic lesion was at least eight weeks old based on volume. Tr. 183; Resp. Ex. M.⁹⁹

I noted that *Cotton et al.* discussed specific variables that affect the accuracy in determining the age of a lesion, including the time between gadolinium injection, the actual imaging which must take place within 29 minutes for maximum enhancement, and the amount of gadolinium used relative to body weight. Tr. 184-85; Resp. Ex. M.¹⁰⁰ Dr. Sriram agreed these factors must be considered in determining the age of a lesion, but he stated all gadolinium scans are done within 30 minutes of injection. Tr. 185, 226-27. He conceded that if the MRI was not done within the required 30 minutes, enhancement would be weaker and could affect the accuracy of the calculations. Tr. 185.

Dr. Sriram explained that different lesions in the same patient develop independently of each other with large variations in duration of enhancement during the acute phase. Tr. 228; Resp. Ex. M at 1.¹⁰¹ "The duration of the enhancement is linearly proportional to the value of the lesion. Large lesions are rare; small lesions are common...when you average them out...[the average] enhancement of a lesion is about two to four weeks." Tr. 229; Resp. Ex. M at 5. It was pointed out to Dr. Sriram that petitioner received the Tdap vaccine on July 12, but the first MRI was not done for another six weeks, placing enhancement of the thoracic lesion within four to six weeks following the Tdap vaccine based on his testimony. Tr. 229. Dr. Sriram agreed the possibility existed that the thoracic lesion began enhancing around the time of the Tdap vaccine, but he stated it would be difficult to measure and calculate volume because it was a spinal cord lesion. Tr. 229-30. He conceded he could only tell how long a lesion lasted—not when it started. Tr. 186, 220-21. He also could not say how long it takes a lesion to enhance "because we do not know what initiates an event." Tr. 187. He added even if it were an infection that triggered a relapse in MS, it is not known how long it would take for an infection to form an acute enhancing lesion because an enhancing lesion can predate clinical evidence of infection, or a subclinical infection can exist. Tr. 187. He could only approximate a timeline of 6-8 weeks. He again conceded that without prior MRIs, he could not say if enhancement began before or after the vaccination. Tr. 219-21.

⁹⁸ Cotton et al., *supra* note 90.

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

Dr. Sriram agreed that enhancing lesions signify a blood brain barrier impairment and that the brain and spine could both be affected at the same rate since the spine is part of the brain. Tr. 230. He agreed relapses are generally associated with enhancing lesions, characterized by inflammation that gadolinium picks up on MRI, though lesions can be enhanced without symptoms. Tr. 226-27. “We cannot conclude that the enhancing lesion that was seen on August 24th represents a reactivation of an old lesion because we do not have an old MRI to compare.” Tr. 231.

Dr. Sriram then conceded *Cotton et al.* discussed only brain lesions—not spinal cord lesions. Tr. 231-32; Resp. Ex. M.¹⁰² Therefore, his calculations were based on petitioner’s non-enhanced brain lesions, not on her enhanced lesion on the thoracic spine “...because we don’t have good data on spinal cord enhancement.” Tr. 232; *see also* Resp. Ex. L. “[W]e have to extrapolate the length of the lesion in the spinal cord with that of the brain”, which is feasible given that the blood brain barrier is the same in the brain and spinal cord. Tr. 230. Further, the MRI images were “very, very weakly enhancing” so they were “probably on the downside of resolution” rather than on the upside. Tr. 232. However, he disagreed that enhancement could occur within 24 hours of a trigger “because we do not know what trigger to give to make that measurement.” Tr. 187-88.

In conclusion, Dr. Sriram stated it would not matter whether the lesion developed before or after the vaccine because the vaccine could not have influenced her course of illness either way. Tr. 240-41. Petitioner “follows the very difficult course of a relapsing-remitting MS patient.” Tr. 241. Dr. Sriram concluded that the Tdap vaccine did not cause petitioner’s MS because onset occurred too quickly after vaccination and a causal mechanism was lacking. Tr. 188, 233.

V. Applicable Legal Standards

a. Legal Standard Regarding Causation

The Vaccine Act provides two avenues for petitioners to receive compensation. First, a petitioner may demonstrate a “Table” injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the provided time period. § 11(c)(1)(C)(i). “In such a case, causation is presumed.” *Capizzano v. Sec’y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed on the Vaccine Injury Table, a petitioner may demonstrate an “off-Table” injury, which requires that the petitioner “prove by a preponderance of the evidence that the vaccine at issue caused the injury.” *Capizzano*, 440 F.3d at 1320; *see* § 11(c)(1)(C)(ii). Initially, a petitioner must provide evidence that he or she suffered, or continues to suffer, from a definitive injury. *Broekelschen v. Sec’y of Health & Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010). A petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the alleged injury; showing that the vaccination was a “substantial factor” and a “but for” cause of the injury is sufficient for recovery. *See Pafford v. Sec’y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Shyface v. Sec’y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999).

¹⁰² Cotton et al., *supra* note 90.

To prove causation for an “off-Table” injury, petitioners must satisfy the three-pronged test established in *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioners show by preponderant evidence that a vaccination petitioner received caused his or her injury “by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.” *Id.* at 1278. Together, these prongs must show “that the vaccine was ‘not only a but-for cause of the injury but also a substantial factor in bringing about the injury.’” *Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373, 1379 (Fed. Cir. 2012) (quoting *Shyface*, 165 F.3d at 1352-53). Causation is determined on a case-by-case basis, with “no hard and fast *per se* scientific or medical rules.” *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Petitioners are not required to identify “specific biological mechanisms” to establish causation, nor are they required to present “epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities.” *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). “[C]lose calls regarding causation are resolved in favor of injured claimants.” *Althen*, 418 F.3d at 1280.

Each of the *Althen* prongs requires a different showing. The first *Althen* prong requires petitioner to provide a “reputable medical theory” demonstrating that the vaccines received *can* cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citation omitted). To satisfy this prong, petitioner’s “theory of causation must be supported by a ‘reputable medical or scientific explanation.’” *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). This theory need only be “legally probable, not medically or scientifically certain.” *Id.* at 1380 (emphasis omitted) (quoting *Knudsen*, 35 F.3d at 548); *see also Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019). Nevertheless, “petitioners [must] proffer trustworthy testimony from experts who can find support for their theories in medical literature.” *LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1341 (Fed. Cir. 2014).

The second *Althen* prong requires proof of a “logical sequence of cause and effect.” *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1278). In other words, even if the vaccinations can cause the injury, petitioner must show “that it did so in [this] particular case.” *Hodges v. Sec'y of Health & Human Servs.*, 9 F.3d 958, 962 n.4 (Fed. Cir. 1993) (citation omitted). “A reputable medical or scientific explanation must support this logical sequence of cause and effect,” *id.* at 961 (citation omitted), and “treating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury,” *Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d at 1375). Petitioner is not, however, required “to eliminate alternative causes as part of establishing [their] *prima facie* case.” *Doe v. Sec'y of Health & Human Servs.*, 601 F.3d 1349, 1357-58 (Fed. Cir. 2010); *see Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1152 (Fed. Cir. 2007) (holding that a “petitioner does not bear the burden of eliminating alternative independent potential causes”).

To satisfy the third *Althen* prong, petitioner must establish a “proximate temporal relationship” between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This

“requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder’s etiology, it is medically acceptable to infer causation-in-fact.” *De Bazan v. Sec’y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). Typically, “a petitioner’s failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause.” *Id.* However, “cases in which onset is too soon” also fail this prong; “in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked.” *Id.*; *see also Locane v. Sec’y of Health & Human Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) (“[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.”).

A petitioner may also be eligible for compensation if the vaccinee had a preexisting condition which was significantly aggravated by a vaccine. *See* § 11(c)(1)(C). In considering a significant aggravation claim for an on-Table injury, the Federal Circuit placed the most significance on whether petitioner’s symptoms began within the time period proscribed. *Whitecotton v. Sec’y of Health & Human Servs.*, 81 F.3d 1099, 1107 (Fed. Cir. 1996) (“Instead of asking whether the person’s symptoms would have occurred absent the vaccine, our test hoves (sic) close to the statutory mandate, and relieves a petitioner of the burden of proving causation if she can show that the first symptom or manifestation of the significant aggravation of her condition occurred within the table time period provided in the statute.”).

For a significant aggravation claim for an off-Table injury, the petitioner’s burden is expanded to six elements, requiring petitioner to show, by preponderant evidence, proof of

- (1) the person’s condition prior to administration of the vaccine, (2) the person’s current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person’s current condition constitutes a “significant aggravation” of the person’s condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving ex rel. Loving v. Sec’y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). The fourth, fifth, and sixth factors are derived from *Althen* prongs one, two, and three, respectively. *Id.* The Federal Circuit has agreed with this approach. *See W.C. v. Sec’y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (“We hold that the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims.”)

However, the third *Loving* factor, determining whether the person suffered a “significant aggravation” of his or her condition, leads to the question of what constitutes a significant aggravation. Based on the legislative history and the language of the statute, it appears that Congress intended for a “significant aggravation” of a condition to present rather dramatically. *See* H.R. Rep. 908, 99th Cong.2d Sess. 1, reprinted in 1986 USCCAN 6287, 6356 (“This [significant aggravation] provision does not include compensation for conditions which might legitimately be

described as preexisting (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), *but is meant to encompass serious deterioration* (e.g., a child with monthly seizures who, after vaccination, has seizures on a daily basis” (emphasis added)); *see also* 42 U.S.C. § 300aa-33(4) (“The term “significant aggravation” means any change for the worse in a preexisting condition which results in *markedly greater* disability, pain, or illness accompanied by *substantial deterioration* of health” (emphases added)).

Once a petitioner has established that his or her condition worsened post-vaccination, the special master must determine “whether the change for the worse in [petitioner’s] clinical presentation was aggravation or a natural progression” of the preexisting condition. *Hennessey*, 2009 WL 1709053 at *42. In doing so, special masters have relied on evidence supporting the “typical” clinical course of the petitioner’s condition. *See, e.g., Sharpe v. Sec’y of Health & Human Servs.*, 964 F.3d 1072, 1086 (Fed. Cir. 2020) (Special master’s determination that petitioner failed to meet *Loving* prong 5 because her seizures began prior to vaccination was set aside); *Faoro v. Sec’y of Health & Human Servs.*, No. 10-704V, 2016 WL 675491, at *27 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), *mot. for review denied*, 128 Fed. Cl. 61 (Fed. Cl. Apr. 11, 2016) (finding that “the vaccinations would not have changed her clinical course and thus, the vaccinations did not significantly aggravate her preexisting condition”).

b. Legal Standard Regarding Fact Finding

The process for making determinations in Vaccine Program cases regarding factual issues begins with analyzing the medical records, which are required to be filed with the petition. § 11(c)(2). Medical records created contemporaneously with the events they describe are generally considered to be more trustworthy. *Cucuras v. Sec’y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993); *but see Kirby v. Sec’y of Health & Human Servs.*, 993 F.3d 1378, 1382-83 (Fed. Cir. 2021) (clarifying that *Cucuras* does not stand for proposition that medical records are presumptively accurate and complete). While not presumed to be complete and accurate, medical records made while seeking treatment are generally afforded more weight than statements made by petitioner after-the-fact. *See Gerami v. Sec’y of Health & Human Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013) (finding that contemporaneously documented medical evidence was more persuasive than the letter prepared for litigation purposes), *mot. for rev. denied*, 127 Fed. Cl. 299 (2014). Indeed, “where later testimony conflicts with earlier contemporaneous documents, courts generally give the contemporaneous documentation more weight.” *Campbell ex rel. Campbell v. Sec’y of Health & Human Servs.*, 69 Fed. Cl. 775, 779 (2006); *see United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1948).

Despite the weight afforded medical records, special masters are not bound rigidly by those records in determining facts such as the onset of a petitioner’s symptoms. *Vallenzuela v. Sec’y of Health & Human Servs.*, No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); *see also Eng v. Sec’y of Health & Human Servs.*, No. 90-175V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb 18, 1994) (explaining that § 13(b)(2) “must be construed so as to give effect to § 13(b)(1) which directs the special master or court to consider the medical record...but does not require the special master or court to be bound by them”); *see also Burns v. Sec’y of Health & Human Servs.*, 3 F.3d 415, 417 (Fed. Cir. 1993) (holding that it is within the special master’s

discretion to determine whether to afford greater weight to medical records or to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is rational).

There are situations in which compelling oral testimony may be more persuasive than written records. *See Campbell*, 69 Fed. Cl. at 779. When witness testimony contradicts medical records, such testimony must be consistent, clear, cogent, and compelling to be persuasive. *See Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *3 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) (vacated on other grounds, *Sanchez by & through Sanchez v. Sec'y of Health & Human Servs.*, No. 2019-1753, 2020 WL 1685554 (Fed. Cir. Apr. 7, 2020), review denied, *Sanchez by & through Sanchez v. Sec'y of Health & Hum. Servs.*, 152 Fed. Cl. 782 (2021)) (quoting *Blutstein v. Sec'y of Health & Human Servs.*, No. 90-2808V, 1998 WL 408611, at *85 (Fed. Cl. Spec. Mstr. June 30, 1998)); *see, e.g., Stevenson ex rel. Stevenson v. Sec'y of Health & Human Servs.*, No. 90-2127V, 1994 WL 808592, at *7 (Fed. Cl. Spec. Mstr. June 27, 1994) (crediting the testimony of a fact witness whose “memory was sound” and “recollections were consistent with the other factual evidence”). Special masters may also consider other types of evidence, such as unsworn statements, on the grounds that the Vaccine Program was designed to have “flexible and informal standards of admissibility of evidence.” 42 U.S.C. § 300aa-12(d)(2)(B); *see also Munn v. Sec'y of Health & Human Servs.*, 970 F.2d 863, 873 (Fed. Cir. 1992).

In short, “the record as a whole” must be considered. § 13(a).

c. Evaluating Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). The Supreme Court’s opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. “In short, the requirement that an expert’s testimony pertain to ‘scientific knowledge’ establishes a standard of evidentiary reliability.” *Id.* at 590 (citation omitted). Thus, for Vaccine Act claims, a “special master is entitled to require some indicia of reliability to support the assertion of the expert witness.” *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). The *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) (“uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted”). Where both sides offer expert testimony, a special master’s decision may be “based on the credibility of the experts and the relative persuasiveness of their competing theories.” *Broekelschen*, 618 F.3d at 1347 (citing *Lampe*, 219 F.3d at 1362). And nothing requires the acceptance of an expert’s conclusion “connected to existing data only by the *ipse dixit* of the expert,” especially if “there is simply too great an analytical gap between the data and the opinion proffered.” *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

d. Consideration of Medical Literature

Finally, although this Ruling discusses some but not all of the literature in detail, the undersigned reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) (“We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision.”); *Simanski v. Sec'y of Health & Human Servs.*, 115 Fed. Cl. 407, 436 (2014) (“[A] Special Master is ‘not required to discuss every piece of evidence or testimony in her decision.’” (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Discussion

There is no dispute that petitioner had preexisting, asymptomatic MS with lesions on her spinal cord and brain, one of which was activated following her receipt of the Tdap vaccine. The parties disagree that the Tdap vaccine was a substantial factor in triggering petitioner’s asymptomatic MS lesion into a clinically symptomatic lesion. Therefore, the case must be decided under *Loving*.

a. *Althen* Prong 1/ *Loving* Prong 4: Petitioner Has Provided a Reputable Medical Theory for How a Tdap Vaccine Can Significantly Aggravate an Asymptomatic Multiple Sclerosis Lesion into Becoming Active.

To satisfy *Althen* Prong 1 / *Loving* Prong 4, petitioner must provide a reputable medical theory as to how the Tdap vaccine could significantly aggravate a person’s asymptomatic lesions, triggering them to clinical manifestation. Petitioner’s theory here is that the Tdap vaccine caused an inflammatory response which triggered the onset of symptoms in a person with pre-existing but latent MS lesions. Tr. 75, 202, 235-36, 248. The theory is based animal studies and literature that support that innate immune responses to infection can cause relapses in MS and vaccines are constructed to elicit a comparable immune response to that of the wild virus. Therefore, vaccines like infections can cause relapses in MS. Tr. 41, 74-75, 106-07; Pet. Ex. 13 at 3-4; Pet. Ex. 15 at 5,¹⁰³ Pet. Ex. 49 at 1-2; Pet. Ex. 53 at 1127;¹⁰⁴ Pet. Ex. 81 at 1; Pet. Ex. 99;¹⁰⁵ Pet. Ex. 102 at 9.¹⁰⁶ Petitioner did not suggest that infections or vaccines can cause MS, only that any agent, even a mild infection, that is capable of causing inflammation in the brain or spinal cord can aggravate existing MS. Tr. 41-42, 106; Pet. Ex. 13 at 5. This can occur from any combination of events that is potentially inflammatory in a susceptible person. Tr. 41-42. Relapses can either be a manifestation of new symptoms, a worsening of existing symptoms, or both. Tr. 44.

Dr. Kinsbourne stated both the medical community and literature accept and support that infections and vaccines can cause inflammation that triggers an MS relapse. Tr. 42-44, 47-48, 105;

¹⁰³ Agmon-Levin et al., *supra* note 13.

¹⁰⁴ Shoenfeld, *supra* note 18.

¹⁰⁵ Buljevac et al., *supra* note 17.

¹⁰⁶ Shoenfeld, *supra* note 18.

Pet. Ex. 49 at 3; Pet. Ex. 99 at 953.¹⁰⁷ *Balofsky et al.* wrote that adverse events from vaccines include the rare severe reaction of hypersensitivity, induction of actual infection, or autoimmune phenomena. Pet. Ex. 17.¹⁰⁸ *Buljevac et al.* concluded that "... at least in the [relapsing/remitting] phase, the level of inflammatory activity influences the extent of structural brain damage. . . Thus, *any factor* that increases inflammatory activity could contribute to neurological deterioration." Pet. Ex. 99 at 953 (emphasis added).¹⁰⁹ *Libbey et al.* showed that infections can trigger a relapse of MS, demonstrating that "[d]isease potentiation could occur indirectly through nonspecific stimulation of immune responses." Tr. 105-06; Pet. Ex. 102.¹¹⁰

Dr. Kinsbourne explained that the tetanus toxoid contained in the Tdap vaccine is a potent immunogen that stimulates a rapid outpouring of proinflammatory cytokines, notably TNF alpha, IL-1 beta, IL-1 alpha, and IL-6. Pet. Ex. 13 at 5; Pet. Ex. 101. He offered several articles in support of this opinion. *Fernandez et al.* showed that the Tdap vaccine increases cytokine levels. Tr. 101; Pet. Ex. 101.¹¹¹ *Kashiwagi et al.* showed that inflammatory activation after infection was similar to inflammatory activation the first day after vaccination. Tr. 50-51, 55; Pet. Ex. 81 at 2; Pet. Ex. 106.¹¹² *Kaplin et al.* showed that pathological specimens taken from TM patients included astrocytes shown to produce IL-6 in response to direct stimulation by proinflammatory cytokines like TNF- α and IL-1 β , viral and bacterial pathogens, and neurotransmitters concluding that, "[p]otential triggers include an immune response following vaccination or an antecedent infection that could involve mechanisms such as...superantigen-mediated inflammation." Pet. Ex. 13 at 5; Pet. Ex. 27 at 2733.¹¹³ *Merson* found that the outpouring of proinflammatory cytokines generated by the innate immune system could trigger an MS relapse, even without a previous exposure to the Tdap antigen. Pet. Ex. 31.¹¹⁴ Finally, *Hofer & Campbell* found the destructive nature of IL-6 can cause immunoinflammatory disease, demyelination, and axonal damage in the spinal cord. Pet. Ex. 13 at 9; Pet. Ex. 26.¹¹⁵

Dr. Kinsbourne also relied on Dr. Sriram's animal studies to support his opinion that the inflammation generated from an infection or vaccination could trigger MS lesions. Pet. Ex. 49 at 2. *Bright & Sriram* determined that MS might be the result of an autoimmune process triggered by an infectious agent. Pet. Ex. 49 at 2; Pet. Ex. 50.¹¹⁶ *Deng & Sriram* concluded that the presentation of neuronal autoantigens to autoreactive T cells and the attendant secretion of cytokines were thought to facilitate the inflammatory process in MS. Pet. Ex. 49 at 2; Pet. Ex. 100 at 239.¹¹⁷ *Patawe & Sriram* concluded that "[v]iral and bacterial infections have been shown to

¹⁰⁷ Buljevac et al., *supra* note 17.

¹⁰⁸ Balofsky et al., *supra* note 35.

¹⁰⁹ Buljevac et al., *supra* note 17.

¹¹⁰ Libbey et al., *supra* note 37.

¹¹¹ Fernandez et al., *supra* note 19.

¹¹² Kashiwagi et al., *supra* note 26.

¹¹³ Kaplin et al., *supra* note 27.

¹¹⁴ Merson, *supra* note 15.

¹¹⁵ Hofer & Campbell, *supra* note 16.

¹¹⁶ Bright & Sriram, *supra* note 28.

¹¹⁷ Deng & Sriram, *supra* note 30.

be associated with disease exacerbations" in relapsing remitting multiple sclerosis. Pet. Ex. 49 at 2; Pet. Ex. 52.¹¹⁸

Dr. Byers agreed that vaccines, like infection, can cause an inflammatory response in the body sufficient to provoke a flare or relapse of MS in a susceptible person. Tr. 135. She explained that following vaccination, cytokines produced in the periphery and released through inflammation can cross the blood brain barrier, activate astrocytes and microglial cells, which then produce more cytokines, primarily IL-6 and IL-17, causing demyelination.¹¹⁹ Pet. Ex. 47 at 3-4; Pet. Ex. 60;¹²⁰ Pet. Ex. 80 at 3-4; Pet. Ex. 27;¹²¹ Pet. Ex. 67;¹²² Pet. Ex. 107.¹²³

Dr. Byers stated that for over 40 years, animal studies have demonstrated the effects of this inflammatory process. Tr. 157-58. For example, MRIs performed after LPS injection in *Serres et al.* showed "new recruitment of inflammatory cells" within 24 hours of injection, suggesting that infectious diseases more than likely activate disease activity in MS, "either directly by the generic response to cell bacterial cell-wall products (LPS and analogs) or indirectly via secondary enhancement of an overactive immune response". Tr. 120-24, 157-58; Pet. Ex. 107 at 5, 7-8.¹²⁴

Dr. Byers added that the pertussis toxin in combination with incomplete Freund's adjuvant and PLP is widely used as an adjuvant in animal studies to induce PLP-specific IL-17 producing CD4+ cells in the periphery causing EAE. Pet. Ex. 80 at 2. Dr. Byers acknowledged that *Buljevac et al.* did not discuss vaccines, but it showed that infection can exacerbate MS. Tr. 146-47; Pet. Ex. 99 at 955.¹²⁵ Likewise, *Barnett & Prineas* showed exacerbation of MS lesions after respiratory infection. Tr. 138, 141-44; Pet. Ex. 47 at 2, 5; Pet. Ex. 105 at 460-61.¹²⁶

Dr. Byers concluded that the inflammatory process, whether by infection or vaccination, can activate inactive lesions as a result of the innate cytokine activation of cells—namely macrophages, T cells, and B cells—that are already present in the quiescent lesions. Tr. 162. Each of these cells can cause demyelination by damaging neurons and are characteristic of MS. Tr. 162-63.

Dr. Sriram's opinions focused primarily on Tdap not causing MS or demyelination. Resp. Ex. J at 2-3; Pet. Ex. 60;¹²⁷ Pet. Ex. 67.¹²⁸ However, Dr. Sriram agreed that activated T cells can migrate to the CNS and activate microglia, which release pro-inflammatory cytokines that can

¹¹⁸ Pawate & Sriram, *supra* note 32.

¹¹⁹ Dr. Byers added that the controversy regarding whether cytokines can breach the blood brain barrier has ended and it is now known that certain cells present in the CNS are activated by astrocytes after systemic stimulation. Tr. 122-23, 144-45; Pet. Ex. 60.

¹²⁰ Gruber et al., *supra* note 52.

¹²¹ Kaplin et al., *supra* note 27.

¹²² Petković & Castellano, *supra* note 51.

¹²³ Serres et al., *supra* note 43.

¹²⁴ *Id.*

¹²⁵ Buljevac et al., *supra* note 17.

¹²⁶ Barnett & Prineas et al., *supra* note 74.

¹²⁷ Gruber et al., *supra* note 52.

¹²⁸ Petković & Castellano, *supra* note 51.

have a toxic effect on oligodendrocytes and neurons and are a prominent component for development of relapses of MS. Resp. Ex. A at 4; Resp. Ex. H.¹²⁹

He disagreed that the cytokines activated in response to the receipt of a Tdap vaccine can cause peripheral inflammation or demyelination in MS; activate the innate immune system causing the release of IL-17; cross the BBB activating astrocytes to produce IL-6; result in the production of hydrogen peroxide causing demyelination; or that oligodendrocytes act to provide nutritional support. Resp. Ex. J at 4-5. Rather, Dr. Sriram maintained that the innate immune system is neuroprotective and reduces inflammation. *Id.*; Resp. Ex. P.¹³⁰

It was explained to Dr. Sriram during the hearing that petitioner was not saying the Tdap vaccine caused her MS but caused an inflammatory response in the innate immune system which triggered the onset of symptoms in a person with pre-existing MS lesions. Tr. 202, 235-36, 248.

Dr. Sriram agreed acute worsening of MS is sometimes preceded by infection. Resp. Ex. A at 3. However, he disagreed that infections and vaccinations are the same because vaccines do not replicate the way an infection does. Tr. 188-89, 199-200; Resp. Ex. K at 2. Dr. Sriram agreed that his own studies propose the role for infections in MS, but not vaccines as a trigger for MS, adding there is no known cause for MS or MS relapses and nothing in the literature or epidemiology supports Tdap vaccine causing either. Tr. 188, 205, 210, 221-23, 226, 238-39; Resp. Ex. K at 2; Pet. Ex. 53.¹³¹ He contended that vaccines are recommended for those with MS and no literature exists to support vaccines worsening MS. Resp. Ex. A at 3-4; Resp. Ex. G.¹³²

While disagreeing that a Tdap vaccine could generate an inflammatory response sufficient to cause an MS relapse, Dr. Sriram agreed vaccines cause an immune response with some degree of inflammation regionally in the lymph nodes after vaccination. Tr. 202, 236, 241-42. Live vaccines can cause a systemic response including fevers, chills, body aches, and pain because an attenuated bug is introduced to the body. Tr. 243. He agreed that sometimes an adjuvant used in the vaccine to amplify the immune response can produce some degree of inflammation usually at the site of the injection, but vaccines do not result in pathogenic illness. Tr. 243-44. Dr. Sriram agreed there is an increased cytokine response in 24 or 48 hours after vaccination but not a “massive increase” sufficient to cause demyelination. Tr. 237.

Dr. Sriram agreed that whether live or attenuated, a vaccine drives an innate immune response which is the reason for the systemic effect. Tr. 245-46. He then explained that the innate immune system is a mechanism by which the body gets ready to fight, and whether an attenuated or heat killed virus vaccine is injected, the body recognizes a foreign pathogen, and the receptors mount an inflammatory response to get rid of it. Tr. 246. He agreed if petitioner had the Tdap vaccine before, the response would be quicker, but he referred to *Fernandez et al.* to show that the timing of an immune response would depend on when the prior Tdap was received. Tr. 246-47;

¹²⁹ Frohman et al., *supra* note 79.

¹³⁰ L.S. Group, *supra* note 85.

¹³¹ Shoenfeld, *supra* note 18.

¹³² Rutschmann et al., *supra* note 78.

Pet. Ex. 101.¹³³ Further, he pointed out that petitioner did not report any local reaction to her vaccine, so if she had an inflammatory response, it was mild. Tr. 244.

Dr. Sriram stated that no evidence exists to support cytokines as pathogenic in MS, submitting that what is known about the pathogenesis of MS is from in vitro testing. Tr. 209-10. He discussed the articles relied on by petitioner from this perspective, stating that *Graber et al.* showed no statistical difference in IL-17 and IL-6 secreted by the T cells between MS patients and healthy controls. Tr. 176-78; Pet Ex. 60 at 27.¹³⁴ *Kashiwagi et al.* did not support the idea that cytokines produced from vaccination can negatively impact the CNS. Tr. 208-09; Pet. Ex. 106.¹³⁵ *Hapfelmeier et al.* showed that vaccines, specifically Tdap, delayed onset of or reduced susceptibility to MS. Tr. 191-94; Resp. Ex. S.¹³⁶ *DeStefano et al.* found similar results, but on a smaller scale. Tr. 194; Resp. Ex. E.¹³⁷ *Rutschmann et al.* suggested that “tetanus vaccine does not increase the risk of relapses in patients with MS.” Tr. 196-97; Resp. Ex. G.¹³⁸ “So all these vaccines . . . for some reason are able to reduce the incidence of multiple sclerosis.” Tr. 194.

Dr. Sriram concluded that petitioner’s experts failed to provide a biological process by which a Tdap vaccine can induce an MS relapse by activating the innate immune system. Resp. Ex. K at 2. Specifically, there is no evidence that relapses in MS are mediated exclusively by activation of innate immune pathways; no evidence of a cytokine “storm” induced by the Tdap vaccine in less than 24 hours that can target the CNS without causing any systemic side effects; no evidence that cytokines cause demyelination; and no evidence that Tdap vaccines induce the kind of cytokines suggested by petitioner’s experts as responsible for clinical relapse. *Id.* at 2-3.

It is petitioner’s burden to “provide a reputable medical or scientific explanation that pertains specifically to petitioner’s case”. *Broekelschen v. Sec’y of Health & Human Servs.*, 618 F.3d 1339, 1345 (Fed. Cir. 2010). Here, petitioner’s experts submitted that literature shows, and the medical community accepts, that an inflammatory immune reaction to infection is capable of triggering an MS relapse. They posited that vaccines are designed to elicit a comparable immune response. Therefore, vaccines like infection can cause a relapse in MS. Tr. 106-07; Pet. Ex. 13 at 4; Pet. Ex. 15 at 5; Pet. Ex. 49 at 1; Pet. Ex. 99;¹³⁹ Pet. Ex. 53 at 1127;¹⁴⁰ Pet. Ex. 81 at 1; Pet. Ex. 102 at 9. Any agent, even mild infection that is capable of causing inflammation in the brain or spinal cord can aggravate existing MS. Tr. 41-42, 106; Pet. Ex. 13 at 5. It is a combination of events that is potentially inflammatory in a susceptible person. Tr. 41-42.

Petitioner has provided sufficient evidence that a Tdap vaccine could significantly aggravate existing but quiescent lesions as a result of the body’s inflammatory response to the receipt of the vaccine. Both petitioner and respondent agreed MS relapses can be triggered by the body’s inflammatory response to an infection. Tr. 43-44, 48, 105-06, 138, 141-47, 187, 222, 237-

¹³³ Fernandez et al., *supra* note 19.

¹³⁴ Graber et al., *supra* note 52.

¹³⁵ Kashiwagi et al., *supra* note 26.

¹³⁶ Hapfelmeier et al., *supra* note 45.

¹³⁷ DeStefano et al., *supra* note 33.

¹³⁸ Rutschmann et al., *supra* note 78.

¹³⁹ Buljevac et al., *supra* note 17.

¹⁴⁰ Shoenfeld, *supra* note 18.

39; Pet. Ex. 47 at 5; Pet. Ex. 99;¹⁴¹ Pet. Ex. 105 at 460-61;¹⁴² Resp. Ex. A at 3; Resp. Ex. G at 4-6.¹⁴³ In fact, Dr. Sriram's own studies conclude that “[a]lthough the etiology of MS is unknown, considerable evidence suggests that environmental triggers play a crucial role in the disease.” Pet. Ex. 50.¹⁴⁴ In 2010, Dr. Sriram co-authored an article, which stated in relevant part:

In addition to their possible role as initiators of the disease process, infections have been thought to trigger relapses in RRMS. . . The mechanisms by which infections can trigger relapses are also thought to involve bystander activation or molecular mimicry. . . A review of current literature shows that infectious agents remain a viable trigger for the initiation of the disease pathogenesis in MS. However, the quest for the identification of a specific bacteria or virus has not yet succeeded. *Viral and bacterial infections have also been shown to be associated with disease exacerbations in RRMS.*

Pet. Ex. 52 at 8 (emphasis added).¹⁴⁵

Dr. Sriram stated that relapses following infection are rare. Tr. 238. However, as detailed above, he does not contest that it can and does occur. Petitioner likened the body's response to infection to that of a vaccine, both being foreign antigens that cause an inflammatory response. Further, petitioner's experts persuasively explained that inflammation, whether from infections or vaccines, can trigger an MS relapse in a susceptible person. Tr. 43-45, 48, 105-07, 143-46; Pet. Ex. 47 at 5; Pet. Ex. 99;¹⁴⁶ Pet. Ex. 105 at 460-61.¹⁴⁷ *Buljevac et al., Kashiwagi et al.*, and the IOM support the theory that inflammation, be it from infection or vaccination, may induce autoimmunity resulting in demyelination in a susceptible individual. Tr. 42-43, 50-52, 55; *see* Pet. Ex. 42;¹⁴⁸ Pet. Ex. 81 at 1-2; Pet. Ex. 99 at 953;¹⁴⁹ Pet. Ex. 106 at 680.¹⁵⁰ Petitioner's experts opined cytokines, specifically IL-6 and IL-17, generated in response to the Tdap vaccination can cross the BBB and damage myelin. Tr. 101-02; Pet. Ex. 27;¹⁵¹ Pet. Ex. 47 at 3; Pet. Ex. 60;¹⁵² Pet. Ex. 67;¹⁵³ Pet. Ex. 80 at 3-4; Pet. Ex. 101;¹⁵⁴ Pet. Ex. 107.¹⁵⁵ Tdap vaccination as a cause of MS is not at issue. The issue is whether the Tdap vaccine can cause an inflammatory reaction sufficient to aggravate a pre-existing but latent lesion on the thoracic spine. Dr. Sriram did not deny that infections can cause relapses in MS; he only stated that it is rare. Tr. 238. Thus, it is reasonable

¹⁴¹ Buljevac et al., *supra* note 17.

¹⁴² Barnett & Prineas et al., *supra* note 74.

¹⁴³ Rutschmann et al., *supra* note 78.

¹⁴⁴ Bright & Sriram, *supra* note 28.

¹⁴⁵ Pawate & Sriram, *supra* note 32.

¹⁴⁶ Buljevac et al., *supra* note 17.

¹⁴⁷ Barnett & Prineas et al., *supra* note 74.

¹⁴⁸ Stratton et al., *supra* note 25.

¹⁴⁹ Buljevac et al., *supra* note 17.

¹⁵⁰ Kashiwagi et al., *supra* note 26.

¹⁵¹ Kaplin et al., *supra* note 27.

¹⁵² Gruber et al., *supra* note 52.

¹⁵³ Petković & Castellano, *supra* note 51.

¹⁵⁴ Fernandez et al., *supra* note 19.

¹⁵⁵ Serres et al., *supra* note 43.

that this same process following Tdap vaccine could cause inflammation in the CNS sufficient to activate an existing but quiescent lesion.

Therefore, petitioner has met her burden in presenting a sound and reliable theory causally connecting the vaccination to the aggravation and relapse of her existing but asymptomatic MS. *Althen*, 418 F.3d at 1278; *Loving*, 86 Fed. Cl. at 143-44.

b. *Althen* Prong 2 / *Loving* Prong 5: Petitioner Has Provided a Logical Sequence of Cause and Effect Between the Tdap Vaccine and the Aggravation of Her MS.

As detailed above, petitioner has shown that Tdap vaccination can cause an inflammatory innate immune response sufficient to trigger a latent but present spinal cord MS lesion to symptomatic level. Tr. 43-45, 48, 105-07, 143-46; Pet. Ex. 47 at 5; Pet. Ex. 99;¹⁵⁶ Pet. Ex. 105 at 460-61.¹⁵⁷ *Althen* Prong 2 / *Loving* Prong 5 requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992).

Dr. Sriram maintained that petitioner's enhancing thoracic spinal cord lesion predated the Tdap vaccine because he estimated that it had enhanced for approximately 6-8 weeks. Tr. 219-21. When asked about the average duration of enhancement, Dr. Sriram stated that "the duration of the enhancement is linearly proportional to the value of the lesion. Large lesions are rare; small lesions are common...when you average them out...[the average] enhancement of a lesion is about two to four weeks." Tr. 229; Resp. Ex. M at 5. It was noted that petitioner's MRIs were done 6 weeks after her receipt of the Tdap vaccine and onset of symptoms. Tr. 229. He then admitted that it is difficult to measure and calculate the volume of the lesions in the spinal cord. Tr. 229-30. He could only tell how long a lesion lasted—not when it started. Tr. 186, 220-21. He conceded that without prior MRIs, he could not say when enhancement began Tr. 187-88, 219-21. He also could not say how long it takes a lesion to enhance "because we do not know what initiates an event." Tr. 187. Even if it were an infection that triggered an MS relapse, it is not known how long it takes for an infection to form an acute enhancing lesion because an enhancing lesion can predate clinical evidence of infection, or a subclinical infection can exist. Tr. 187.

Dr. Sriram then conceded that *Cotton et al.* only discussed brain lesions—not spinal cord lesions and that his calculations were based on petitioner's non-enhanced brain lesions, not on her enhanced thoracic spine lesion "...because we don't have good data on spinal cord enhancement." Tr. 231-32; Resp. Ex. M;¹⁵⁸ *see also* Resp. Ex. L. Therefore, "[w]e have to extrapolate the length of the lesion in the spinal cord with that of the brain", which is feasible given that the blood brain barrier is the same in the brain and spinal cord. Tr. 230. Further, the MRI images were "very, very weakly enhancing" so they were "probably on the downside of resolution". Tr. 232. However, he stated he could not point to anything to show that enhancement could occur within 24 hours of a

¹⁵⁶ Buljevac et al., *supra* note 17.

¹⁵⁷ Barnett & Prineas et al., *supra* note 74.

¹⁵⁸ Cotton et al., *supra* note 90.

trigger “because we do not know what triggers to give to make that measurement.” Tr. 187-88, 219-21.

The parties agreed and stipulated that petitioner’s lesions were present prior to vaccination. The parties also agreed that without MRIs prior to the Tdap vaccine, there is no way to tell when and if the subject lesion had enhanced in the past but remained asymptomatic. Regardless, the MRI that showed the enhancing lesion on the thoracic spine was performed six weeks after petitioner received the Tdap vaccine and had an onset of symptoms. The experts agreed that lesions enhance on average between 4-6 weeks. Tr. 69-70, 219-21, 229, 232-33. Therefore, preponderant evidence supports a finding that the spinal cord lesion began enhancing after the Tdap vaccination, resulting in the onset of petitioner’s symptoms.

Petitioner proved by preponderant evidence that the Tdap vaccine could trigger preexisting asymptomatic MS into clinically symptomatic MS. She has also demonstrated how her symptoms and MRI imaging following vaccination correspond with her proposed theory. Thus, petitioner has carried her burden on *Althen* Prong 2 / *Loving* Prong 5. *Althen*, 418 F.3d at 1278; *Loving*, 86 Fed. Cl. at 143-44.

c. *Althen* Prong 3 / *Loving* Prong 6: Petitioner Has Demonstrated a Proximate Temporal Relationship Between the Tdap Vaccine and the Onset of her MS Symptoms.

Next, petitioner must show that the temporal relationship between the Tdap vaccine and the onset of her symptoms was medically reasonable. A central disagreement in this case is the 24-hour onset of petitioner’s symptoms following the Tdap vaccine. Pet. Ex. 47 at 2, 4. Petitioner received the Tdap vaccine at approximately 8am on July 12, 2013 and began feeling pain in her feet and ankles the following morning at around 9am when she awoke and tried to get out of bed. Tr. 40, 70; Pet. Ex. 5 at 5, 39, 41.

Dr. Kinsbourne opined that petitioner was primed for a rapid response having received prior Tdap vaccinations. Pet. Ex. 13 at 8, 9; *see also* Tr. 250-51; Pet. Ex. 49 at 1. *Netea et al.* showed that the innate immune system, like the adaptive immune system, harbors memory allowing for a quicker immune response. Pet. Ex. 13 at 8-9; Pet. Ex. 103 at 678-79.¹⁵⁹ *Kashiwagi et al.* concluded that “[a]ll effective vaccines induce acquired immunity with the development of antigen-specific antibodies and/or cell-mediated immunity, and the stimulation of innate immunity is now considered essential.” Pet. Ex. 106 at 678.¹⁶⁰ Petitioner’s quick response following the vaccination was the result of an anamnestic reaction triggering an existing but asymptomatic MS lesion. Pet. Ex. 13 at 9.

Dr. Byers stated that the rapid onset can be explained as follows: Petitioner already had quiescent MS lesions containing antigen specific cells—macrophages, T cells, and B cells—that were asymptomatic. “[M]ost of the pathology was already in place. The antigen specific cells just had to be triggered.” Pet. Ex. 80 at 2. Reactivation of these lesions was the result of the innate

¹⁵⁹ Netea et al., *supra* note 14.

¹⁶⁰ Kashiwagi et al., *supra* note 26.

immune system producing proinflammatory cytokines, namely IL-6, within hours of the vaccine which can push anti-myelin basic protein specific CD17+ cells—key actors in MS—to maturation and differentiation, quickly triggering petitioner’s MS relapse. Tr. 122-123, 138, 162; Pet. Ex. 47 at 4; Pet. Ex. 80 at 1-2;¹⁶¹ Pet. Ex. 106 at 680.¹⁶² The role of a vaccine is to initiate the adaptive immune system by initially activating the innate immune system. Tr. 152. It is now well accepted that the innate immune system has memory and will react with specificity and intensity. As such, the innate immune response is able to trigger an MS relapse within a day of exposure to a vaccine antigen. Tr. 119, 136-37. Pet. Ex. 47 at 5; Pet. Ex. 64.¹⁶³

Dr. Sriram focused on the Tdap vaccine as the cause of petitioner’s MS lesions and argued that the onset of symptoms was too quick to attribute the development of the lesion to the vaccine. He stated that “tetanus toxoid doesn’t induce an innate immune response because the body does not recognize this as a foreign pathogen. It goes through an adaptive immune response because it’s a foreign protein and you develop an antibody and T cell response...that takes about 14 days for an adaptive immune response to occur if one is not primed and perhaps sooner if one is primed”. Tr. 233-35. He explained that when you receive a Tdap vaccine for the first time, the response in developing antigenic toxoid antibodies takes between 2-3 weeks. If you have received Tdap in the past and are primed or have antibodies, it will take about 7 days for an antibody response to the vaccine. Tr. 204-05, 234-35; Resp. Ex. A at 4; Resp. Ex. H.¹⁶⁴; Resp. Ex. I.¹⁶⁵

Dr. Sriram argued that no reliable evidence exists that the innate immune system alone can drive a relapse in MS or that an adaptive immune system can drive an MS relapse within 24 hours. Tr. 176, 210, 212. “The doubling time of T cells is approximately 24-48 hours, a time frame under which antigen reactive T cells are not likely to expand and migrate to the spinal cord.” Resp. Ex. A at 4. He then agreed if petitioner had the Tdap before, the response would be quicker but would depend on when the prior Tdap was received. Tr. 246-47; Pet. Ex. 101.¹⁶⁶ Dr. Sriram submitted that it took three to four days for mice to get sick in studies where T-lymphocytes were activated against MOG or MBP. Tr. 202-03. Accordingly, he was not persuaded by petitioner’s theory that the immune response could occur within 24 hours. Tr. 202-03. Dr. Sriram agreed that hypersensitivity reactions occur within hours, but an adaptive response triggering demyelination takes more time. Tr. 203.

However, Dr. Sriram later conceded that systemic responses can be seen after a Tdap or DTaP vaccine due to the acellular pertussis component of the vaccine that drives an innate immune response. Tr. 245. He explained that the innate immune system “is a mechanism by which we can get the troops ready right off the bat. So, when we are immunized . . . , our body recognizes these foreign pathogens . . . we have receptors to this to mount an inflammatory response to get rid of it. Even though it’s a dead virus, the body doesn’t know that.” Tr. 246. Thus, Dr. Sriram seemed to

¹⁶¹ *Supra* notes 57 and 65.

¹⁶² Kashiwagi et al., *supra* note 26.

¹⁶³ O’Sullivan et al., *supra* note 66.

¹⁶⁴ Frohman et al., *supra* note 79.

¹⁶⁵ Du et al., *supra* note 80.

¹⁶⁶ Fernandez et al., *supra* note 19.

agree that the Tdap vaccine could in fact induce an innate immune response and do so within 24 hours.

Both parties agree that the onset of petitioner's injury began within 24 hours of her receipt of the Tdap vaccination. Petitioner's experts explained that the innate immune system is now understood to have memory, which allows for the recognition of and quick response to a previously encountered antigen. Pet. Ex. 13 at 8-10; Pet. Ex. 47 at 5; Pet. Ex. 64;¹⁶⁷ Pet. Ex. 72;¹⁶⁸ Pet. Ex. 103 at 678-79;¹⁶⁹ *see also* Tr. 246-47. Petitioner had four prior Tdap vaccines, with the most recent being in 2012, or within the year prior to the subject vaccine. Tr. 250-51. When her immune system encountered the antigen from the subject Tdap vaccine, it was prepared to mount a rapid immune response, accounting for the 24-hour onset of symptoms.

Preponderant evidence supports that an immune-mediated reaction to a new antigen in a person with an intact central nervous system takes at least five days. *See* Pet. Ex. 47 at 4; Tr. 234. However, because petitioner's CNS was both primed by prior Tdap vaccinations and vulnerable because of her subclinical spinal cord and brain lesions, it is medically reasonable that symptoms would manifest more quickly as they did in petitioner.

Petitioner has satisfied *Althen* Prong 3 / *Loving* Prong 6. *Althen*, 418 F.3d at 1278; *Loving*, 86 Fed. Cl. at 143-44.

d. *Loving* Prong 1: Petitioner's Condition Prior to the Tdap Vaccine.

The *Loving* test next requires a determination of petitioner's condition prior to the vaccination she received on July 12, 2013. *Loving*, 86 Fed. Cl. at 143-44. There is no dispute that petitioner had subclinical MS prior to July 12, 2013. *See* Joint Stipulation at 3; Pet. Ex. 47 at 6; Resp. Ex. L at 1. However, prior to the July 12, 2013, petitioner was healthy, active, working full time as a nurse, caring for husband and children, and showing her dog. Pet. Ex. 93 at 2, 4; Tr. 8-9. Petitioner's medical records support no ongoing medical issues at that time.

e. *Loving* Prong 2: Petitioner's Current Condition Following Her Receipt of the Subject Tdap Vaccine.

The next part of the *Loving* test is to discuss "the person's current condition (or condition following the vaccination if that is also pertinent)." *Loving*, 86 Fed. Cl. at 143-44. Petitioner's MS symptoms started on July 13, 2013, the day following her Tdap vaccine and progressed slowly thereafter. Tr. 13, 40, 70; Pet. Ex. 5 at 5, 39, 41; Resp. Ex. L at 1. The experts agreed her MRI films in August 2013 showed enhancing lesions at T6-T7 consistent with her symptoms. Pet. Ex. 1 at 9; Pet. Ex. 5 at 5; Pet. Ex. 13 at 11; Tr. 37-38, 69-70, 76-77, 126-27, 226.

Thereafter, petitioner complained of numbness, burning in her feet, low back pain, headaches, and blurred vision. Pet. Ex. 6 at 2, 5; Pet. Ex. 10 at 2-3; Pet. Ex. 11 at 3. There are no

¹⁶⁷ O'Sullivan et al., *supra* note 66.

¹⁶⁸ Sun et al., *supra* note 67.

¹⁶⁹ Netea et al., *supra* note 14.

medical records filed between the end of December 2014 and MRIs in January 2017. Pet. Ex. 76. Petitioner suffered an onset of worsening ascending numbness and urinary incontinence in March 2017, at which time she was formally diagnosed with RRMS. Pet. Ex. 77; Pet. Ex. 78; Pet. Ex. 94; Pet. Ex. 95.

f. *Loving Prong 3: There was a Significant Aggravation of Petitioner's MS Following her Receipt of the Subject Tdap Vaccine.*

The final prong of the *Loving* test is to determine whether there is a “significant aggravation” of petitioner’s condition by comparing her condition before vaccination to her condition after vaccination. *Loving*, 86 Fed. Cl. at 143-44. The statute defines “significant aggravation” as “any change for the worse in a pre-existing condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health.” § 33(4). Using this definition, the undersigned finds that, based on the facts and circumstances here, petitioner had a significant aggravation of her underlying MS.

Petitioner’s condition clearly became active following the vaccine. The parties stipulated that petitioner had no neurological symptoms prior to her receipt of the July 12, 2013 Tdap vaccination. Joint Stipulation at 1. It is also undisputed that petitioner began to feel pain and numbness on the bottom of her feet the day after the vaccine. *Id.* at 2; Pet. Ex. 2 at 7, 9; Pet. Ex. 5 at 3, 5, 39, 41. Petitioner’s August 2013 MRIs showed enhancement at T6-T7, as well as multiple non-enhancing lesions in the spinal cord and in the brain. Pet. Ex. 1 at 13-14, 16; Pet. Ex. 13 at 6; Pet. Ex. 4 at 10-12, 14-16. Petitioner was initially diagnosed with TM. Pet. Ex. 1 at 9. She improved slightly with IV Solu-Medrol, and repeat MRIs in December 2013 were stable. *Id.*; Pet. Ex. 2 at 11-12; Pet. Ex. 6 at 9, 11, 13. However, petitioner’s numbness and pain persisted. Pet. Ex. 6 at 1, 2, 5; Pet. Ex. 10 at 2; Pet. Ex. 11 at 3, 6. Petitioner affirmed being stable for three years thereafter until a relapse in March 2017. Pet. Ex. 93 at 5.

Following a relapse in March 2017, an MRI revealed multiple spinal cord lesions, including a new enhancing lesion at C3. Pet. Ex. 78 at 3; *see also* Pet. Ex. 94; Pet. Ex. 96. In April 2017, petitioner was noted to have fatigue, visual disturbance, and sleep disturbance. Pet. Ex. 95 at 13-14. She was prescribed Tecfidera. *Id.* at 11-12. In 2018, petitioner was noted to be doing well on Tecfidera but still suffering several falls and near falls. *Id.* at 44, 78-80, 103, 117, 125.

Petitioner described her current condition in detail at the hearing. She testified that she has pain, numbness, and blurry vision. She’s fearful of another relapse and of falling due to her unsteady gait. She has “electric shock pain” in her legs and warm flashes. She had to sell her home and limit her training with her dogs. Tr. 25-26.

Based on her condition prior to the vaccine and her condition subsequently, preponderant evidence supports that petitioner’s pre-vaccination and post-vaccination health, activity, and professional life were markedly different. It is agreed that petitioner had lesions prior to her receipt of the Tdap vaccine. Joint Stipulation at 3. However, she was completely asymptomatic. Dr. Kinsbourne commented that the lesions that existed prior to vaccination may not have ever become symptomatic but for the Tdap vaccine. Tr. 37. Thus, I find that petitioner’s condition following

vaccination constitutes a significant aggravation under the statute. As such, petitioner meets the criterion of *Loving* prong 3.

g. Respondent Has Failed to Meet His Burden to Prove an Alternative Cause Unrelated to the Tdap Vaccination.

Once a petitioner establishes a *prima facie* case, the burden of proof shifts to respondent to prove by a preponderance of the evidence that the “illness, disability, injury, condition, or death described in the petition is due to factors unrelated to the administration of the vaccine described in the petition.” § 13(a)(1)(B); *Walther*, 485 F.3d at 1151. I find that respondent has failed to establish any other cause for the triggering of petitioner’s MS. Viewing respondent’s evidence in its most favorable light, Dr. Sriram opined that vaccinations have not been shown to cause MS or MS relapses. He further stated that the onset here occurred too quickly for it to have been an immune response to the vaccine. Resp. Ex. A at 3-4. Ultimately, Dr. Sriram argued that the cause of MS and MS relapses is unknown and thus, not related to vaccination. *Id.* at 3; Resp. Ex. K at 2.

Dr. Sriram did not provide an alternative explanation for petitioner’s development of symptoms one day after the receipt of the Tdap vaccination other than to say that “[b]y and large, almost all relapses do not have an antecedent cause that we can attribute to.” Tr. 238-39.

The Vaccine Act excludes “any idiopathic, unexplained, unknown, hypothetical, or undocumented cause, factor, injury, illness, or condition” from the “factors unrelated” to the vaccine upon which respondent’s proof may rest. *See generally* § 13. Respondent’s argument that the cause of MS is unknown is insufficient to carry his burden of proving an alternative cause unrelated to vaccination. The fact that the cause of MS relapses remains unknown leaves open the possibility that a vaccine could be a trigger. Accordingly, the medical community has been investigating this possibility for decades.

As explained above, petitioner has provided preponderant evidence that the Tdap vaccine can trigger an MS relapse and did so in this case within a medically acceptable timeframe. Thus, because petitioner has carried her burden in establishing a *prima facie* case of causation, and respondent has failed to establish an alternative cause, petitioner is entitled to compensation.

VII. Conclusion

Upon careful evaluation of all evidence submitted in this matter, I find that petitioner has established entitlement to compensation under the Vaccine Act. Accordingly, this case shall proceed to damages, and a damages order specifying next steps will issue shortly.

IT IS SO ORDERED.

s/ Mindy Michaels Roth
 Mindy Michaels Roth
 Special Master